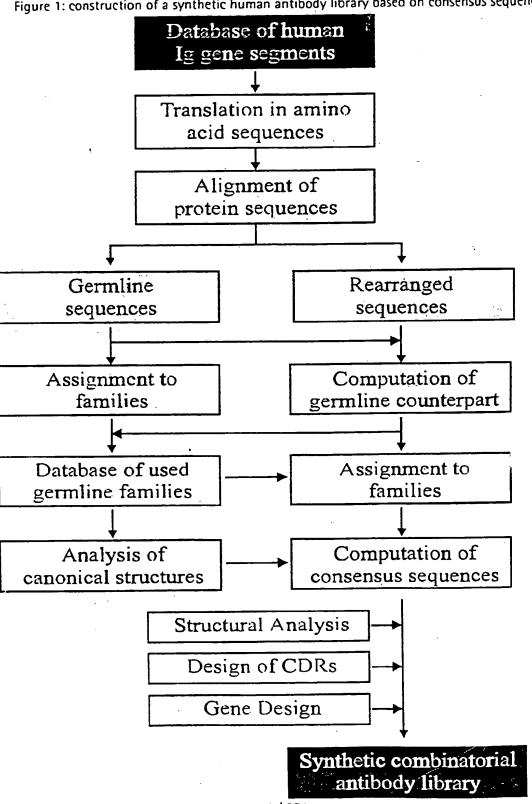
Figure 1: construction of a synthetic human antibody library based on consensus sequences



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Figure 2A: VL kappa consensus sequences

Figure 2A: VL kappa consensus sequences

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Figure 2B: VL lambda consensus sequences

Figure 2B: VL lambda consensus sequences

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Figure 2C: V heavy chain consensus sequences

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CGGTCGTCGA ACGTTTCGCC CCAGGGCAGG GCAAAATCGC CGAGACCTAG Figure 3A: V kappa 1 (Vk1) gene sequence (continued)

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Figure 3B: V kappa 2 (Vk2) gene sequence

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Figure 3B: V kappa 2 (Vk2) gene sequence (continued)

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ഠ CTCCGGGCGA G Д ഗ CTGAGCCTGT Ы ഗ ᆸ ⊟ Ø М BanII Figure 3C: V kappa 3 (Vk3) gene sequence Ø EcoRV ~~~~~

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Figure 3C: V kappa 3 (Vx3) gene sequence (continued)

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Figure 3D: V kappa 4 (Vk4) gene sequence

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| VMTQSPDSLAVSLGE |             |   | TGACCCAGAG      |                      | TESTICE ES  |
| <b>Z</b> i      |             |   |                 |                      | E   |
| >               | >           | <b>)</b>                                | ないようしよくせん       | )                    | 7   |
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CTATAGCACT ACTGGGTCTC GGGCCTATCG

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ATATCGTCGT TATAGCAGCA GAGCGTGCTG CTCGCACGAC ATTAACTGCA GAAGCAGCCA CTTCGTCGGT TAATTGACGT ACGTGCGACC TGCACGCTGG

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TGGTACCAGC AGAAACCAGG TCAGCCGCCG TCTTTGGTCC AGTCGGCGGC ACCATGGTCG CTATCTGGCG GATAGACCGC ACAACAAAA TGTTGTTTT

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TCCCGGATCG AGGCCTAGC CTTTCGCCCC GAAAGCGGGG ATCCACCCGT TAGGTGGGCA TTTATTGGGC AAATAACCCG TTTGATAATT AAACTATTAA

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Figure 3D: V kappa 4 (Vk4) gene sequence (continued)

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ATTTCGTCCC TAAAGCAGGG ATGGGACTGG TACCCTGACC CGTGACTAAA GCACTGATTT TCTGGATCCG AGACCTAGGC AAAATCGCCG TTTTAGCGGC

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AATATGGTGG TTATACCACC CGGTCGTCGT GCCAGCAGCA CACATAATAA GTGTATTATT TCTGCACCGC AGACGTGGCG TGCAAGCTGA ACGTTCGACT

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CATGC GTACG GAAATTAAAC CTTTAATTTG TACGAAAGTT ATGCTTTCAA TTGGCCAGGG GGCGGCTGGA AACCGGTCCC CCGCCGACCT

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CAGGTCAGCG GTCCAGTCGC TCACCGCGTG AGTGGCGCAC GCCTTCAGTG CGGAAGTCAC TGACCCAGCC ACTGGGTCGG GTCTCGCACG CAGAGCGTGC

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GCAGCAGCAG CAACATTGGC GTTGTAACCG CGTCGTCGTC ACACTGGTAG AGCACATCGC TCGTGTAGCG

TGTGACCATC

AGCAACTATG TCGTTGATAC

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CGCCGAAACT GCTGATTTAT GCGGCTTTGA CCCGGGACGG GGGCCCTGCC GGTCGTCAAC TGAGCTGGTA CCAGCAGTTG

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Figure 4A: V lambda 1 (VA.1) gene sequence (continued)

| GCGGATCCAA                                     | SG TCGCAGGGAG TCCGCACGGC CTAGCAAAAT CGCCTAGGTT |
|--|--|
| GATCGTTTTA                                     | CGGC CTAGCAAAT                                 |
| AGGCGTGCCG                                     | TCCGCACGGC                                     |
| CC AGCGTCCCTC AGGCGTGCCG GATCGTTTTA GCGGATCCAA | TCGCAGGGAG                                     |
| GATAACAACC                                     | CTATTGTTGG                                     |

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TCGCTTCTGC AGCGAAGACG CCCGGACGTT GGGCCTGCAA AACGCTAATG TTGCGATTAC AAGCGGCACC AGCGCGAGCC TCGCGCTCGG TTCGCCGTGG

ACACAAACCG TGTGTTTGGC G Į, > GGTGGGGCGG CCACCCGCC Д H ۲ GTCGTAATAT Q H Y CAGCATTATA × Y C Q TTATTGCCAG AATAACGGTC AAGCGGATTA TTCGCCTAAT Ω ø 口

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GGCGCCACGA AGTTAACCGT TCTTGGC CCGCCGTGCT TCAATTGGCA AGAACCG

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AGCGGCTCAC CAGGTCAGAG GTCCAGTCTC TCGCCGAGTG TCGAAGTCAC TGACCCAGCC AGCTTCAGTG Eco57I ACTGGGTCGG GTCTCGCGTG CAGAGCGCAC

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CCGATATTGA GGCTATAACT GCTACACCCG CGATGTGGGC CATGATCGTC GTACTAGCAG GTAATGGTAG AGCACATGCC CATTACCATC TCGTGTACGG

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Figure 4B: V lambda 2 (VA2) gene sequence (continued)

|                             | •     |              |            |                    |
|-----------------------------|-------|--------------|------------|--------------------|
| G N T A S L T I S G L Q A E | BbsI  | CAAGCGGAAG   | TTCGCCTTC  | руус оону ттр ру Б |
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| IJ                          |       | CTG          | GAC        | д                  |
| ග                           |       | SGC          | SCG        | H                  |
| ഗ                           |       | TAGCGGCCTG   |            | H                  |
| H                           |       |              |            | ≯                  |
| E                           |       | CCA          | GGT        | Ħ                  |
| ı                           |       | GCCTGACCAT   | CGGACTGGTA | Ø                  |
|                             |       | 000          | CGG        | Ø                  |
| Ω                           | ٠     |              |            | <i>(</i> )         |
| Ø                           |       | SS           | )<br>(3)   |                    |
| ⊣                           |       | ACC.         | lgG        | ×                  |
| z                           | ,     | AACACCGCGA   | TTGTGGCGCT | <b>&gt;</b>        |
| Ŋ                           |       | 390          | SCG        | Ω                  |
|                             |       |              |            | A                  |
| X<br>S                      | BamHI | ~<br>CAAAAGC | GTTTTCG    | ы<br>ы             |
| 124                         | Ban   | ~ ZA7        | GT.        | D E<br>BbsI        |
|                             |       |              |            |                    |

GCCTGTGTTT CGGACACAAA ATACCACCCC TATGGTGGGG GTCGTCGTAA CAGCAGCATT TTATTATTGC AATAATAACG TGCTTCGCCT ACGAAGCGGA

G G T K L T V L G Hpai MscI

GGCGGCGCA CGAAGTTAAC CGTTCTTGGC CCGCCGCCGT GCTTCAATTG GCAAGAACCG

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Figure 4C: V lambda 3 (VA3) gene sequence

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|----|-------|---|-----------------------|-----------------------|--------|-------------|---------------------------|-------|--------|
| Ø  |       |   | CAGGTCAGAC            | GTCCAGTCTG            |        |             | Ω                         |       |        |
| G  |       | }                                       | GT(                   | CAC                   |        |             | Ø                         |       |        |
| _  | xA1   | ~ | CAG                   | GTC                   |        |             | ×                         |       |        |
| Д  | Se    | <i>₹</i>                                |                       | IG                    | •      |             | *                         |       |        |
| A  |       |   | S                     | CG                    |        |             |                           |       |        |
| >  |       |   | GTJ                   | CAA                   |        |             | Ц                         |       |        |
| ഗ  |       |   | AGCGTTGCAC            | TCGCAACGTG            |        |             | Ŋ                         |       |        |
| >  |       |   |                       |                       |        |             | ᆸ                         |       |        |
| S  |       |   | CAG                   | GTC                   | 57I    | }<br>}<br>} | Ø                         |       |        |
| ф  | SexAI |   | GCCTTCAGTG            | CGGAAGTCAC            | Eco57I | }<br>}      | S C S G D A L G D K Y A S |       |        |
| Д  |       |   |                       |                       |        |             | ტ                         | ٠     |        |
| ŏ  |       |   | AGCTATGAAC TGACCCAGCC | TCGATACTTG ACTGGGTCGG |        |             | Ŋ                         |       |        |
| Ę  |       |   | CCC                   | 999                   |        |             | ပ                         | SI    | 2      |
|    |       |   | TGA                   | ACT                   |        |             | ß                         | BSSSI | ~~~~~~ |
| ᅱ  | •     |   | AC                    | TG                    | •      |             | н                         |       | ?      |
| 口  |       | ٠                                       | 1GA                   | \CT'                  |        |             |                           |       |        |
| S  |       |   | TAI                   | AT/                   | -      |             | A R                       |       |        |
| W  |       |   | AGC                   | TCG                   |        |             | A                         |       |        |

| TACGCGAGCT<br>ATGCGCTCGA   | A D D   | TTATGATGAT<br>AATACTACTA   |
|--|---|--|
| TCGTGTAGCG GCGATGCGCT GGGCGATAAA TACGCGAGCT<br>AGCACATCGC CGCTACGCGA CCCGCTATTT ATGCGCTCGA | I V I   | CAGGCGCCAG TTCTGGTGAT TTATGATGAT GTCCGCGGTC AAGACCACTA AATACTACTA                                |
| GCGATGCGCT   | Q A P V<br>BbeI                                     | CAGGCGCCAG<br>GTCCGCGGTC   |
| TCGTGTAGCG<br>AGCACATCGC   | K P G<br>XmaI                                       | GAAACCCGGG<br>CTTTGGGCCC   |
| CGCGCGTATC<br>GCGCGCATAG   | W Y Q Q K P G Q A P V L V I Y D D<br>KpnI Xmal Bbel | GGTACCAGCA GAAACCCGGG CAGGCGCCAG TTCTGGTGAT TTATGATGAT CCATGGTCGT CTTTGGGCCC GTCCGCGGTC AAGACCAA |

Figure 4C: V lambda 3 (VA.3) gene sequence (continued)

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CCAACAGCGG GGTTGTCGCC TTTAGCGGAT AAATCGCCTA GGGCCTTGCG CCCGGAACGC GGAGTCCGTA CCTCAGGCAT AGACTGGCAG TCTGACCGTC

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CTGCTTCGCC GACGAAGCGG TCAGGCGGAA AGTCCGCCTT AATCGCCGTG TTAGCGGCAC TGGGACTGGT ACCCTGACCA GTTGTGGCGC CAACACCGCG

ACCGCCGCCG TGGCGGCGGC Ö Ö GCGGACACAA CGCCTGTGTT > വ Д ATATGGTGGG TATACCACCC ⊱ Q Q H CCAGCAGCAT GGTCGTCGTA ATTATTAG TAATAATAAC × ×

T K L T V L G Hpal MscI ACGAAGTTAA CCGTTCTTGG C TGCTTCAATT GGCAAGAACC C

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CGGCCAGCAG GCCCGTCGTC CACTTTTTG GTGAAAAAAC ACCGCGCCTT TGGCGCGGAA ACCAAGTCAG TGGTTCAGTC CAGGTGCAAT GTCCACGTTA

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AGCTATGCGA TCGATACGCT GTGAAAATCG CACTTTTAGC GGAGGCCTCC CCTCCGGAGG TCGACGTTTC AGCTGCAAAG CGTGAAAGTG GCACTTTCAC

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CTACCCGCCG GATGGGCGGC CAGAGCTCAC GTCTCGAGTG GGACCCGTCC CCTGGGCAGG CGCGGTTCGG GCGCCAAGCC TTAGCTGGGT AATCGACCCA

A'Q K F Q G R GCGCAGAAGT TTCAGGGCCG CGCGTCTTCA AAGTCCCGGC GGCGAACTAC CCGCTTGATG X N Ą TTTTTGGCAC AAAAACCGTG ഗ ഥ TAATAAGGCT ATTATTCCGA Д

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Figure 5A: V heavy chain 1.A (VH1A) gene sequence (continued)

ATGGAACTGA TACCTTGACT CACCGCGTAT GTGGCGCATA TTTCGTGGTC AAAGCACCAG TGGCGCCTAC ACCGCGGATG CCACTGGTAA GGTGACCATT

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CGCAACCCCG GCGTTGGGGC TAATAACGCG ATTATTGCGC TGCCGGCACA ACGCCCGTGT ATCGCTTCTA GCAGCCTGCG TAGCGAAGAT CGTCGGACGC

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GGGACCACTG CCCTGGTGAC GGCCAAGGCA CCGGTTCCGT GGATTATTGG CCTAATAACC GGCGATGGCT TTTATGCGAT AAATACGCTA CCGCTACCGA

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BlpI

GGTTAGCTCA CCAATCGAGT

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Figure 58: V heavy chain 18 (VH1B) gene sequence

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CGGGCGCGAG CCCGCGCTC CACTTTTTG GTGAAAAAAC GCCCCCCTT CGGCGCGGAA CAGGTGCAAT TGGTTCAGAG ACCAAGTCTC GTCCACGTTA

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TCGATAATAT AGCTATTATA CCTCCGGATA TACCTTTACC GGAGGCCTAT ATGGAAATGG TCGACGTTTC AGCTGCAAAG GCACTTTCAC CGTGAAAGTG

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GATGGGCTGG CTACCCGACC CAGAGCTCAC GTCTCGAGTG CCTGGGCAGG GGACCCGTCC GGCGGTTCGG CCGCCAAGCC ACGTGACCCA TGCACTGGGT

TTCAGGGCCG CGCGTCTTCA AAGTCCCGGC G Ø GCGCAGAAGT Õ CACGAACTAC GTGCTTGATG Z ATAGCGGCGG C TATCGCCGCC G Z TAATTGGGCT ATTAACCCGA Д

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|   | M T R D T S I S T A Y M E L |                                       | ATGGAACTGA<br>TACCTTGACT |  |
|---|-----------------------------|---------------------------------------|--------------------------|--|
|   | X                           |                                       | GTAT A                   |  |
|   | T                           |                                       | CACCGCGTAT               |  |
|   | H                           |                                       | CCAGCATTAG<br>GGTCGTAATC |  |
| ontinued)                                   | E S                         |                                       | CCAGO                    |  |
| y chain 1B (VH1B) gene sequence (continued) | д<br>О                      |                                       | ACCCGTGATA<br>TGGGCACTAT |  |
| IB (VH1B) ge                                | E                           |                                       |                          |  |
| Figure 5B: V heavy chain 1                  | V T M<br>BstEII             | \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | GGTGACCATG<br>CCACTGGTAC |  |
|   |                             |                                       |                          |  |

CGCAACCCCG BSSHII ATTATTGCGC TAATAACGCG TGCCGGCACA ACGGCCGTGT EagI CGTCGGACGC ATCGCTTCTA GCAGCCTGCG TAGCGAAGAT

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CCCTGGTGAC GGGACCACTG CCGGTTCCGT GGCCAAGGCA GGATTATTGG CCTAATAACC TTTATGCGAT AAATACGCTA GGCGATGGCT CCGCTACCGA

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GGTTAGCTCA

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GCTGGGTTTG CTGGTGAAAC CGACCCAAAC GACCACTTTG CAGGTGCAAT TGAAAGAAAG CGGCCCGGCC GICCACGITA ACTITCITIC GCCGGGCCGG

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TTTCCGGATT TAGCCTGTCC ACGTCTGGCG TGCAGACCGC ATCGGACAGG TGGACATGGA AAAGGCCTAA ACCTGTACCT CCTGACCCTG GGACTGGGAC

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TIGGCGIGGG CIGGATICGC CAGCCGCCIG GGAAAGCCCT CGAGIGGCIG CCTTTCGGGA GCTCACCGAC GACCTAAGCG GTCGGCGGAC AACCGCACCC

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CGGACTTTTG GCCTGAAAAC TATAGCACCA ATATCGTGGT ACTATTCATA GCTCTGATTG ATTGGGATGA TGATAAGTAT CGAGACTAAC TAACCCTACT

| N Q V L T |      |               | ATCAGGTG GTGCTGACTA | TTTAGTCCAC CACGACTGAT   |
|-----------|------|---------------|---------------------|---|
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| ÞΥ        | NspV | 11111         | GAZ                 | CTJ   |
| ഗ         |      |               | LTC                 | 4AG   |
| Ħ         |      | •             | TAC                 | TATGAAGCTT  |
| Ω         |      |               | G A                 | E<br>U  |
| ×         |      |               | AAA                 | TLL   |
| വ         |      |               | AGC                 | TCG   |
| Н         |      |               | ATT                 | TGG TAATCGTTTC  |
| 터         |      |               | ACC                 | TGG   |
| Ц         |      |               | TG                  | 3AC   |
| ĸ         | MluI | 1 1           | GCGT                | CGCAGAC   |
|           |      | L T I S K D I | д<br>н≀             | L T I S K D T S K N Q V  I  CTGACC ATTAGCAAAG ATACTTCGAA AAATCAGGTG |

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CGCGCGTTGG GCGCGCAACC CCTATTATTG GGATAATAAC GATACGGCCA CTATGCCGGT ACTGGTTGTA CCTGGGCCAC GGACCCGGTG TGACCAACAT

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CGTGGGACCA GCACCCTGGT TGGGGCCAAG ACCCCGGTTC CTACCTAATA GCTTTTATGC GATGGATTAT CGAAAATACG CCGCCGCTAC GGCGGCGATG

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GACGGTTAGC TCAG CTGCCAATCG AGTC Figure 5D: V heavy chain 3 (VH3) gene sequence

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CGGGGGGCAG GCCGCCGTC CTGGTGCAAC GACCACGTTG ອວວອວວອວວອ ວອອວອອວອວ CTTCACGTTA ACCACCTTTC TGGTGGAAAG GAAGTGCAAT

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AGCTATGCGA TCGATACGCT TACCTTTAGC ATGGAAATCG CCTCCGGATT GGAGGCCTAA AGCTGCGCGG TCGACGCGCC CCTGCGTCTG GGACGCAGAC

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GGTGAGCGCG CCACTCGCGC GTCTCGAGTG CAGAGCTCAC GCGCCAAGCC CCTGGGAAGG CGCGGTTCGG GGACCCTTCC ACTCGACCCA TGAGCTGGGT

GCGGATAGCG TGAAAGGCCG CGCCTATCGC ACTITCCGGC ტ × > ഗ Ω Ø CACCTATTAT GTGGATAATA × ⊱ I S G S G G S ATTAGCGGTA GCGGCGG CGCCGCCGTC TAATCGCCAT

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Figure 5D: V heavy chain 3 (VH3) gene sequence (continued)

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| SRDN       | PmlI | 11111     |
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| Н          |      |           |
| E          |      |           |
| ഥ          |      |           |

CTGCAAATGA TAAGCTTTTT GTGGACATA GACGTTTACT ATTCGAAAAA CACCCTGTAT TCACGTGATA AAAATGGTAA AGTGCACTAT TTTTACCATT

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ATTATTGCGC GCGTTGGGGC TAATAACGCG CGCAACCCCG TGCCGGCACA ACGCCCGTGT TGTCGGACGC ACGCCTTCTA ACAGCCTGCG TGCGGAAGAT

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CCCTGGTGAC GGGACCACTG CCGGTTCCGT GGCCAAGGCA CCTAATAACC GGATTATTGG GGCGATGGCT TTTATGCGAT CCGCTACCGA AAATACGCTA

V S S BlpI GGTTAGCTCA

CCAATCGAGT

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Figure 5E: V heavy chain 4 (VH4) gene sequence

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CGAGCGAAAC GCTCGCTTTG CTGGTGAAAC GACCACTTTG TGGTCCGGGC ACCAGGCCCG TGCAAGAAAG ACGTTCTTTC GTCCACGTTA CAGGTGCAAT

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AGCTATTATT TCGATAATAA CAGCATTAGC GTCGTAATCG TTTCCGGAGG AAAGGCCTCC ACCTGCACCG TGGACGTGGC CCTGAGCCTG GGACTCGGAC

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GATTGGCTAT CTAACCGATA GTCTCGAGTG CAGAGCTCAC CCTGGGAAGG GGACCCTTCC GGAGCTGGAT TCGCCAGCCG AGCGGTCGGC CCTCGACCTA

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CCGAGCCTGA AAAGCCGGGT TTTCGGCCCA GGCTCGGACT CAACTATAAT GTTGATATTA ATTTATTATA GCGGCAGCAC CGCCGTCGTG TAAATAATAT

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Figure 5E: V heavy chain 4 (VH4) gene sequence (continued)

|                               |        |         | ·          | H             |
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| n<br>S                        |        |         | ₹GC        | rcg           |
| _                             |        |         | ACTG       | TG7           |
| ×                             |        |         | AAA        |               |
| Н                             |        |         | CTG        | GAC           |
| လ                             |        |         | AGC        | TCG           |
| TIS V D T S K N Q F S L K L S |        |         | GTTTAGCC   | CAAATCGG      |
| Ø                             |        |         | CA         | GT            |
| z                             |        |         | AAC        | TTG           |
| ×                             | >      | 1 1     | CGAAAAACCA | GCTTŢTTGGT    |
| വ                             | NspV   | 1 1     |            |               |
| ₽                             |        | į       | TTGATACTT  | TGAA          |
| Ω                             |        |         | GAI        | AACTATG       |
| >                             |        |         | U          | $\mathcal{O}$ |
| လ                             |        |         | AGC        | TCG           |
| Н                             | ΙΙ     |         | ATT        | TAA           |
| H                             | BStEII | 1 2 2 2 | GACCATT    | CTGGTAATCG    |

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| TTGGGGGGGC<br>AACCCCGCCG           | F Y A M D Y W G Q G T L V T V |
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| ATTGCGCGCG<br>TAACGCGCGC           | <b>O</b> 4                    |
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| TGT                                | ×                             |
| GCCGTGTATT<br>CGGCACATAA           | ≯                             |
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| ATA<br>TAT                         | Σ                             |
| CGGC GGCGGATACG<br>GCCG CCGCCTATGC | A                             |
| <u>ပ</u> ပ                         | ×                             |
| 5005<br>0860                       | ĬΉ                            |
| CGTGA                              | വ                             |
| ე <u>ეე</u>                        | Ω                             |
| 311565:5:                          |                               |

TTATTGGGGC CAAGGCACCC TGGTGACGGT GTTCCGTGG ACCACTGCCA AATAACCCCG ATGCGATGGA TACGCTACCT GATGGCTTTT CTACCGAAAA

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S S BlpI TAGCTCAG

ഗ ഥ G Д 又 又  $\gt$ ഥ Ø G Figure 5F: V heavy chain 5 (VH5) gene sequence ഗ Ø  $\gt$ 口 Ø >

CGGGCGAAAG GCCCCCTTTC CACTTTTTG GTGAAAAAAC ACCAAGICIC GCCGCGCTI CGGCGCGGAA GAAGTGCAAT TGGTTCAGAG MfeI CTTCACGTTA

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AGCTATTGGA TCGATAACCT GTTCCGGATA TTCCTTTACG CAAGGCCTAT AAGGAAATGC TCGACGTTTC CCTGAAAATT AGCTGCAAAG GGACTTTTAA

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CTACCCGTAA GATGGGCATT CAGAGCTCAC GTCTCGAGTG GGACCCTTCC CCTGGGAAGG CGCGGTCTAC GCGCCAGATG AACCGACCCA TTGGCTGGGT

Ø TCTCCGAGCT TTCAGGGCCA AGAGGCTCGA AAGTCCCGGT ഗ Ø S Ы ഗ ATGGGCAATA TACCCGTTAT × ĸ E GCGATAGCGA CGCTATCGCT ഗ Ω Ģ TAAATAGGCC ATTTATCCGG Ы  $\succ$ 

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Figure SF: V heavy chain 5 (VHS) gene sequence (continued)

Ø Е S ഗ × Ω Ø ഗ BStEII

CTTCAATGGA GAAGTTACCT AGCGCGGATA AAAGCATTAG CACCGCGTAT GTGGCGCATA TTTCGTAATC TCGCGCCTAT GGTGACCATT CCACTGGTAA

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ATTATTGCGC GCGTTGGGGC CGCAACCCCG TAATAACGCG ACGGCCATGT TGCCGGTACA TCGCTCGCTA GCAGCCTGAA AGCGAGCGAT CGTCGGACTT

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CCCTGGTGAC GGGACCACTG GGCCAAGGCA CCGGTTCCGT GGATTATTGG CCTAATAACC TTTATGCGAT AAATACGCTA GGCGATGGCT CCGCTACCGA

V S S BlpI

GGTTAGCTCA G CCAATCGAGT C

Figure 5G: V heavy chain 6 (VH6) gene sequence

Е Ø ഗ Д × Ы G Д G ഗ Ø Ø MfeI Ø

CGAGCCAAAC GCTCGGTTTG CTGGTGAAAC GACCACTTTG TGGTCCGGGC ACCAGGCCCG TGCAACAGTC GICCACGITA ACGITGICAG CAGGTGCAAT

ഗ Z ഗ ഗ ഗ BSPEI G ഗ Ø O Е S Ы

TITCCGGAGA TAGCGTGAGC AGCAACAGCG TCGTTGTCGC ATCGCACTCG AAAGGCCTCT ACCTGTGCGA TGGACACGCT CCTGAGCCTG GGACTCGGAC

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CTGGATTCGC CAGTCTCCTG GGCGTGGCCT CGAGTGGCTG CCGCACCGGA GCTCACCGAC GTCAGAGGAC GACCTAAGCG CGGCGTGGAA GCCGCACCTT

~~~~~

TIGCTAATAC GCCACTCGCA AACGATTATG CGGTGAGCGT ഗ > Ω Z CAAATGGTAT GTTTACCATA 3 × ATTATCGTAG CCGCCATGGA TAATAGCATC S K GCCGTACCT ۳ 24

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| sednen     | Н   | H     | <b>? ?</b>                              |
| genes      | ⊣   | BsaBI | \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \   |
| (VHb)      | Н   | m     | ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ |
| vy chain   | K   |       | <b>?</b>                                |
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| Figure 5G: | ×   |       |   |
|            |     |       |   |

CAGTTTAGCC GTCAAATCGG TGGGCCTATG AAGCTTTTTG TTCGAAAAAC ACCCGGATAC TAATGGTAGT ATTACCATCA CTTTTCGGCC GAAAAGCCGG

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TTATTGCGCG GCCGGCACAT AATAACGCGC CGGCCGTGTA CCGGAAGATA GGCCTTCTAT GTCGCACTGG CAGCGTGACC TGCAACTGAA ACGTTGACTT

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G G GATTATTGGG GCCAAGGCAC CGGTTCCGTG CTAATAACCC TTATGCGATG AATACGCTAC GCGATGGCTT CGCTACCGAA CGTTGGGGCG GCAACCCCGC

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GTTAGCTCAG CAATCGAGTC CCTGGTGACG GGACCACTGC

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 $\alpha$ 

BSSHII

WO 97/08320 PCT/EP96/03647

Figure 6: oligonucleotides for gene synthesis

- **O1K1** 5'- GAATGCATACGCTGATATCCAGATGACCCAGAG-CCCGTCTAGCCTGAGC -3'
  - **O1K2** 5'- CGCTCTGCAGGTAATGGTCACACGATCACCCAC-GCTCGCGCTCAGGCTAGACGGGC -3'
  - **01K3** 5'- GACCATTACCTGCAGAGCGAGCCAGGGCATTAG-CAGCTATCTGGCGTGGTACCAGCAG -3'
  - **01K4** 5'- CTTTGCAAGCTGCTGGCTGCATAAATTAATAGT-TTCGGTGCTTTACCTGGTTTCTGCTGGTACCACGCCAG -3'
- **O1K5** 5'- CAGCCAGCAGCTTGCAAAGCGGGGTCCCGTCCC-GTTTTAGCGGCTCTGGATCCGGCACTGATTTTAC -3'
- **O1K6** 5'- GATAATAGGTCGCAAAGTCTTCAGGTTGCAGGC-TGCTAATGGTCAGGGTAAAATCAGTGCCGGATCC -3'
- **02K1** 5'- CGATATCGTGATGACCCAGAGCCCACTGAGCCT-GCCAGTGACTCCGGGCGAGCC -3'
- **O2K2** 5'- GCCGTTGCTATGCAGCAGGCTTTGGCTGCTTCT-GCAGCTAATGCTCGCAGGCTCGCCCGGAGTCAC--3'
- **O2K3** 5'- CTGCTGCATAGCAACGGCTATAACTATCTGGAT-TGGTACCTTCAAAAACCAGGTCAAAGCCC -3'
- **O2K4** 5'- CGATCCGGGACCCCACTGGCACGGTTGCTGCCC-AGATAATTAATAGCTGCGGGCTTTGACCTGGTTTTTG -3'
- **02K5** 5'- AGTGGGGTCCCGGATCGTTTTAGCGGCTCTGGA-TCCGGCACCGATTTTACCCTGAAAATTAGCCGTGTG -3'
- **O2K6** 5'- CCATGCAATAATACACGCCCACGTCTTCAGCTT-CACACGCCTAATTTTCAGGG -3'
- O3K1 5'- GAATGCATACGCTGATATCGTGCTGACCCAGAG-CCCGG -3'
- O3K2 5'- CGCTCTGCAGCTCAGGGTCGCACGTTCGCCCGG-AGACAGGCTCAGGGTCGCCGGGCTCTGGGTCAGC -3'
- O3K3 5'- CCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCA-GCAGCTATCTGGCGTGGTACCAG -3'

Figure 6: (continued)

- O3K4 5'- GCACGGCTGCTCGCGCCATAAATTAATAGACGC-GGTGCTTGACCTGGTTTCTGCTGGTACCACGCCAGATAG -3'
- O3K5 5'- GCGCGAGCAGCCGTGCAACTGGGGTCCCGGCGC-GTTTTAGCGGCTCTGGATCCGGCACGGATTTTAC -3'
- O3K6 5'- GATAATACACCGCAAAGTCTTCAGGTTCCAGGC-TGCTAATGGTCAGGGTAAAATCCGTGCCGGATC -3'
- **O4K1** 5'- GAATGCATACGCTGATATCGTGATGACCCAGAG-CCCGGATAGCCTGGCG -3'
- O4K2 5'- GCTTCTGCAGTTAATGGTCGCACGTTCGCCCAG-GCTCACCGCCAGGCTATCCGGGC -3'
- **O4K3** 5'- CGACCATTAACTGCAGAAGCAGCCAGAGCGTGC-TGTATAGCAGCAACAACAAAACTATCTGGCGTGGTACCAG -
- **O4K4** 5'- GATGCCCAATAAATTAATAGTTTCGGCGGCTGA-CCTGGTTCTGCTGGTACCACGCCAGATAG -3'
- **O4K5** 5'- AAACTATTAATTTATTGGGCATCCACCCGTGAA-AGCGGGGTCCCGGATCGTTTTAGCGGCTCTGGATCCGCAC-3'
- **O4K6** 5'- GATAATACACCGCCACGTCTTCAGCTTGCAGGG-ACGAAATGGTCAGGGTAAAATCAGTGCCGGATCCAGAGCC -3'
- **O1L1** 5'- GAATGCATACGCTCAGAGCGTGCTGACCCAGCC-GCCTTCAGTGAGTGG -3'
- O1L2 5'- CAATGTTGCTGCTGCTGCCGCTACACGAGATGG-TCACACGCTGACCTGGTGCGCCACTCACTGAAGGCGGC -3'
- **O1L3** 5'- GGCAGCAGCAGCAACATTGGCAGCAACTATGTG-AGCTGGTACCAGCAGTTGCCCGGGAC -3'
- O1L4 5'- CCGGCACGCCTGAGGGACGCTGGTTGTTATCAT-AAATCAGCAGTTTCGGCGCCCGTCCCGGGCAACTGC -3'
- O1L5 5'- CCCTCAGGCGTGCCGGATCGTTTTAGCGGATCC-AAAAGCGGCACCAGCGCGAGCCTTGCG -3'

Figure 6: (continued)

O1L6 5'- CCGCTTCGTCTTCGCTTTGCAGGCCCGTAATCG-CAAGGCTCGCGCTGG -3'

- **O2L1** 5'- GAATGCATACGCTCAGAGCGCACTGACCCAGCC-AGCTTCAGTGAGCGGC -3'
- **O2L2** 5'- CGCTGCTAGTACCCGTACACGAGATGGTAATGC-TCTGACCTGGTGAGCCGCTCACTGAAGCTGG -3'
- **O2L3** 5'- GTACGGGTACTAGCAGCGATGTGGGCGGCTATA-ACTATGTGAGCTGGTACCAGCAGCATCCCGG -3'
- **O2L4** 5'- CGCCTGAGGGACGGTTGCTCACATCATAAATCA-TCAGTTTCGGCGCCCTTCCCGGGATGCTGCTGGTAC -3'
- **O2L5** 5'- CAACCGTCCCTCAGGCGTGAGCAACCGTTTTAG-CGGATCCAAAAGCGGCAACACCGCGAGCC -3'
- **O2L6** 5'- CCGCTTCGTCTTCCGCTTGCAGGCCGCTAATGG-TCAGGCTCGCGGTGTTGCCG -3'
- **O3L1** 5'- GAATGCATACGCTAGCTATGAACTGACCCAGCC-GCCTTCAGTGAGCG -3'
- O3L2 5'- CGCCCAGCGCATCGCCGCTACACGAGATACGCG-CGGTCTGACCTGGTGCAACGCTCACTGAAGGCGGC -3'
- **O3L3** 5'- GGCGATGCGCTGGGCGATAAATACGCGAGCTGG-TACCAGCAGAAACCCGGGCAGGCGC -3'
- **O3L4** 5'- GCGTTCCGGGATGCCTGAGGGACGGTCAGAATC-ATCATAAATCACCAGAACTGGCGCCTGCCCGGGTTTC -3'
- **O3L5** 5'- CAGGCATCCCGGAACGCTTTAGCGGATCCAACA-GCGGCAACACCGCGACCCTGACCATTAGCGG -3'
- **O3L6** 5'- CCGCTTCGTCTTCCGCCTGAGTGCCGCTAATGG-TCAGGGTC -3'
- O1246H1 5'- GCTCTTCACCCCTGTTACCAAAGCCCAG-GTGCAATTG -3'
- **O1AH2** 5 ' GGCTTTGCAGCTCACTTTCACGCTGCTGCCCGG-TTTTTTCACTTCCGCGCCAGACTGAACCAATTGCACCTGGGC-TTTG -3'

Figure 6: (continued)

**O1AH3** 5 ' - GAAAGTGAGCTGCAAAGCCTCCGGAGGCACTTT-TAGCAGCTATGCGATTAGCTGGGTGCGCCAAGCCCCTGGGCAG GGTC -3 '

- O1AH45'- GCCCTGAAACTTCTGCGCGTAGTTCGCCGTGCC-AAAAATCGGAATAATGCCGCCCATCCACTCGAGACCCTGCCC-AGGGGC -3'
- **O1AH5**5'- GCGCAGAAGTTTCAGGGCCGGGTGACCATTACC-GCGGATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCG -3'
- **Olabh6** 5'- GCGCGCAATAATACACGGCCGTATCTTCGCT-ACGCAGGCTGCTCAGTTCC -3'
- **O1BH2** 5 ' GGCTTTGCAGCTCACTTTCACGCTCGCGCCCGG-TTTTTTCACTTCCGCGCCGCCTCTGAACCAATTGCACCTGGGC-TTTG -3 '
- **O1BH4** 5 ' GCCCTGAAACTTCTGCGCGTAGTTCGTGCCGCC-GCTATTCGGGTTAATCCAGCCCATCCACTCGAGACCCTGCCCACGGGGC -3 '
- **O1BH5** 5 ' GCGCAGAAGTTTCAGGGCCGGGTGACCATGACC CGTGATACCAGCATTAGCACCGCGTATATGGAACTGAGCAGCC TGCG -3 '
- **O2H3** 5'- CTGACCCTGACCTGTACCTTTTCCGGATTTAGC-CTGTCCACGTCTGGCGTTGGCGTGGGCTGGATTCGCCAGCCGCCTGGGAAAG -3'
- **O2H4** 5'- GCGTTTTCAGGCTGGTGCTATAATACTTATCAT-CATCCCAATCAATCAGAGCCAGCCACTCGAGGGCTTTCCCAGGCGCTGG -3'

Figure 6: (continued)

- **O2H5** 5'- GCACCAGCCTGAAAACGCGTCTGACCATTAGCA-AAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACAT
- **02H6** 5'- GCGCGCAATAATAGGTGGCCGTATCCACCGGGT-CCATGTTGGTCATAGTCAGC -3'
- O3H1 5'- CGAAGTGCAATTGGTGGAAAGCGGCGGCCCT-GGTGCAACCGGCCGCCAG -3'
- O3H2 5'- CATAGCTGCTAAAGGTAAATCCGGAGGCCGCGC-AGCTCAGACGCAGGCTGCCGCCCGGTTGCAC -3'
- O3H3 5'- GATTTACCTTTAGCAGCTATGCGATGAGCTGGG-TGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAG -3'
- O3H4 5'- GGCCTTTCACGCTATCCGCATAATAGGTGCTGC-CGCCGCTACCGCTAATCGCGCTCACCCACTCGAGACCC -3'
- **O3H5** 5'- CGGATAGCGTGAAAGGCCGTTTTACCATTTCAC-GTGATAATTCGAAAAAACACCCTGTATCTGCAAATGAACAG-3'
- **O3H6** 5'- CACGCGCGCAATAATACACGGCCGTATCTTCCG-CACGCAGGCTGTTCATTTGCAGATACAGG -3'
- **O4H2** 5'- GGTCAGGCTCAGGGTTTCGCTC TTTCACCAG-GCCCGGACCACTTTCTTGCAATTGCACCTGGGCTTTG -3'
- **O4H3** 5'- GAAACCCTGAGCCTGACCTGCACCGTTTCCGGA-GGCAGCATTAGCAGCTATTATTGGAGCTGGATTCGCCAGCCGC-3'
- **O4H5** 5'- CGGCAGCACCAACTATAATCCGAGCCTGAAAAG-CCGGGTGACCATTAGCGTTGATACTTCGAAAAACCAGTTTAGCCTG-3'
- **O4H6** 5'- GCGCGCAATAATACACGGCCGTATCCGCCGCCG-TCACGCTGCTCAGTTTCAGGCTAAACTGGTTTTTCG -3'

Figure 6: (continued)

- O5H1 5'- GCTCTTCACCCCTGTTACCAAAGCCGAAGTGCAATTG -3'.
- **O5H2** 5'- CCTTTGCAGCTAATTTTCAGGCTTTCGCCCGGT-TTTTTCACTTCCGCGCCGCTCTGAACCAATTGCACTTCGGCTTTGG -3'
- **O5H3** 5'- CCTGAAAATTAGCTGCAAAGGTTCCGGATATTC-CTTTACGAGCTATTGGATTGGCTGGGTGCGCCAGATGCCTGG -3'
- **O5H4** 5'- CGGAGAATAACGGGTATCGCTATCGCCCGGATA-AATAATGCCCATCCACTCGAGACCCTTCCCAGGCATCTGGCGCAC-3'
- **O5H5** 5'- CGATACCCGTTATTCTCCGAGCTTTCAGGGCCA-GGTGACCATTAGCGCGGATAAAAGCATTAGCACCGCGTATCTTC-3'
- **O5H6** 5'- GCGCGCAATAATACATGGCCGTATCGCTCGCTT-TCAGGCTGCTCCATTGAAGATACGCGGTGCTAATG -3'
- **O6H2** 5'- GAAATCGCACAGGTCAGGCTCAGGGTTTGGCTC-GGTTTCACCAGGCCCGGACCAGACTGTTGCAATTGCACCTGG-GCTTTG -3'
- **O6H3** 5'- GCCTGACCTGTGCGATTTCCGGAGATAGCGTGA-GCAGCAACAGCGCGGGGGGAACTGGATTCGCCAGTCTCCTGGGCG-3'
- **O6H4** 5'- CACCGCATAATCGTTATACCATTTGCTACGATA-ATAGGTACGGCCCAGCCACTCGAGGCCACGCCCAGGAGACTG-GCG-3'
- **O6H5** 5'- GGTATAACGATTATGCGGTGAGCGTGAAAAGCC-GGATTACCATCAACCCGGATACTTCGAAAAACCAGTTTAGCCTGC -3'
- **O6H6** 5'- GCGCGCAATAATACACGGCCGTATCTTCCGGGG-TCACGCTGTTCAGTTGCAGGCTAAACTGGTTTTTC -3'
- OCLK1 5 ' GGCTGAAGACGTGGGCGTGTATTATTGCCAGCA-GCATTATACCACCCGCCGACCTTTGGCCAGGGTAC 3 '
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Figure 6: (continued)

- OCLK2 5 '- GCGGAAAAATAAACACGCTCGGAGCAGCCACCG-TACGTTTAATTTCAACTTTCGTACCCTGGCCAAAGGTC -3'
- OCLK3 5 '- GAGCGTGTTTATTTTTCCGCCGAGCGATGAACA-ACTGAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTG -3 '
- OCLK4 5 '- CAGCGCGTTGTCTACTTTCCACTGAACTTTCGC-TTCACGCGGATAAAAGTTGTTCAGCAGGCACACCACGC -3 '
- OCLK5 5 '- GAAAGTAGACAACGCGCTGCAAAGCGGCAACAG-CCAGGAAAGCGTGACCGAACAGGATAGCAAAGATAG -3 '
- OCLK6 5 '- GTTTTTCATAATCCGCTTTGCTCAGGGTCAGGG-TGCTGCTCAGAGAATAGGTGCTATCTTTGCTATCCTGTTCG -
- OCLK7 5 '- GCAAAGCGGATTATGAAAAACATAAAGTGTATG-CGTGCGAAGTGACCCATCAAGGTCTGAGCAGCCCGGTG -3'
- OCLK8 5 '- GGCATGCTTATCAGGCCTCGCCACGATTAAAAG-ATTTAGTCACCGGGCTGCTCAGAC -3'
- OCH1 5'- GGCGTCTAGAGGCCAAGGCACCCTGGTGACGGT-TAGCTCAGCGTCGAC -3'
- OCH2 5'- GTGCTTTTGCTGCTCGGAGCCAGCGGAAACACG-CTTGGACCTTTGGTCGACGCTGAGCTAACC -3'
- **OCH3** 5'- CTCCGAGCAGCAAAAGCACCAGCGGCGCACGG-CTGCCTGGGCTGCCTGGTTAAAGATTATTTCC -3'
- OCH4 5'- CTGGTCAGCGCCCCGCTGTTCCAGCTCACGGTG-ACTGGTTCCGGGAAATAATCTTTAACCAGGCA -3'
- OCH5 5'- AGCGGGGCGCTGACCAGCGGCGTGCATACCTTT-CCGGCGGTGCTGCAAAGCAGCGGCCTG -3'
- OCH6 5'- GTGCCTAAGCTGCTGCTCGGCACGGTCACAACG-CTGCTCAGGCTATACAGGCCGCTGCTTTGCAG -3'
- OCH7 5'- GAGCAGCAGCTTAGGCACTCAGACCTATATTTG-CAACGTGAACCATAAACCGAGCAACACC -3'
- OCH8 5'- GCGCGAATTCGCTTTTCGGTTCCACTTTTTAT-CCACTTTGGTGTTGCTCGGTTTATGG-3'

Figure 7A: sequence of the synthetic Ck gene segment

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GCGATGAACA CGCTACTTGT TTTCCGCCGA AAAGGCGGCT CGTGTTTATT GCACAAATAA GACGAGGCTC CTGCTCCGAG CGTACGGTGG GCATGCCACC

TTGAAAATAG AACTTTTATC CCTGCTGAAC GGACGACTTG Z ᆸ CGCACCACAC SCGTGGTGTG > S CCGTGCCGCT GGCACGGCGA Ø Н G ACTGAAAAGC TGACTTTTCG လ ×

CGTTTCGCCG TGGAAAGTAG ACAACGCGCT GCAAAGCGGC r Ø TGTTGCGCGA Ø Z Ω ACCTTTCATC > × 3 GAAAGTTCAG CTTTCAAGTC > CGCGTGAAGC GCGCACTTCG 回 ഷ Д

GCACCTATTC CGTGGATAAG S AGCAAAGATA TCGTTTCTAT Ω × ഗ GCTTGTCCTA CGAACAGGAT Ø ьı AACAGCCAGG AAAGCGTGAC TTTCGCACTG H > വ 团 TTGTCGGTCC Ø ഗ

TTTGTATTTC AAACATAAAG 耳 × CCTAATACTT GGATTATGAA 团 ⊱⊣ Ω TGGGACTGGG ACTCGTTTCG ACCCTGACCC TGAGCAAAGC × ഗ Н Н ы E TCTGAGCAGC AGACTCGTCG ഗ S Ы

Figure 7A: sequence of the synthetic Ck gene segment (continued)

CCACTGATTT GGTGACTAAA J S S P TGAGCAGCCC Ö 回 TGTATGCGTG ACATACGCAC

SFNRGEA

Sphi

StuI

TCTTTTAATC GTGGCGAGGC CTGATAAGCA TGC AGAAAATTAG CACCGCTCCG GACTATTCGT ACG

Figure 78: sequence of the synthetic CH1 gene segment

S S Д Ø 口 Д لتا > S Д G  $\bowtie$ ₽ Sal A BlpI TCCGAGCAGC AAGGCGACCG AGGCTCGTCG TTCCGCTGGC GGTTCGCACA CCAAGCGTGT CTGGTTTCCA GCTCAGCGTC GACCAAAGGT CGAGTCGCAG

GGCTGCCTGG TTAAAGATTA CCGACGGACC AATTTCTAAT C ဟ GGCTGCCCTG CCGACGGGAC Ø K CGCCGCCGTG GCGCCGCCAC ഗ ഗ TTTCGTGGT AAAAGCACCA ʬ ഗ 又

GACTGGTCGC CTGACCAGCG GICGCCCCGC CAGCGGGGCG ഗ ഗ CCAGTCACCG TGAGCTGGAA ACTCGACCTT Z 3 ഗ GGTCAGTGGC > Д TTTCCCGGAA AAAGGGCCTT Ē Д ഥ

GTATAGCCTG CACGACGITT CGTCGCCGGA CATATCGGAC GCAGCGGCCT ഗ ഗ ഗ GTGCTGCAAA о П GAAAGGCCGC CTTTCCGGCG Д GCGTGCATAC CGCACGTATG 工 က

TTAGGCACTC AGACCTATAT TCTGGATATA Ø AATCCGTGAG ტ GAGCAGCAGC CTCGTCGTCG S ഗ ഗ TGACCGTGCC TCGTCGCAAC ACTGGCACGG > > AGCAGCGTTG > ഗ S

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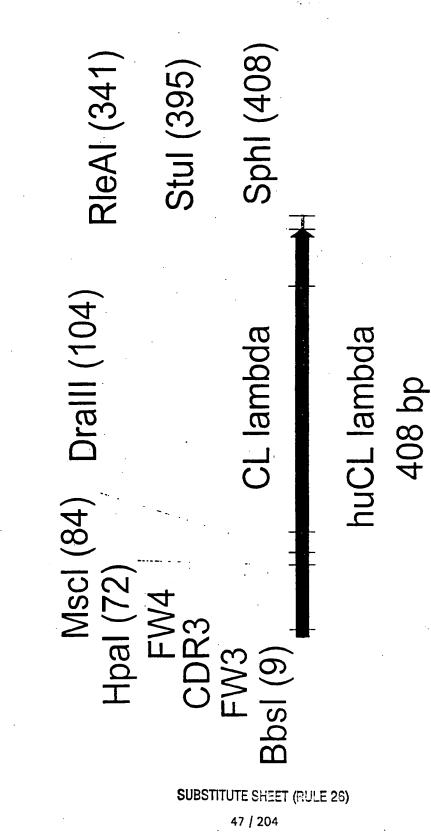
Figure 78: sequence of the synthetic CH1 gene segment (continued)

AAAAAAGTGG GTTTCACCTA CAAAGTGGAT Ω X AACCATAAAC CGAGCAACAC GCTCGTTGTG Z . ග Ы TTGGTATTTG 又 五 Z AACGTTGCAC TTGCAACGTG Z ပ

E P K S E F \* HindIII

AACCGAAAAG CGAATTCTGA TAAGCTT TTGGCTTTTC GCTTAAGACT ATTCGAA

Figure 7C: functional map and sequence of module 24 comprising the synthetic CA gene segment (huCL lambda)



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Figure 7C: functional map and sequence of module 24 comprising the synthetic Cl gene segment (huCL lambda) (continued)

|     | BbsI   |            |                            |                                  |            |
|-----|--|------------|----------------------------|----------------------------------|------------|
| -   | CAAGACGAAG CGGATTATTA                                  | ATTATTA    | TTGCCAGCAG                 | CATTATACCA CCCCGCCTGT            | CCCCCCCTGT |
|     | CTTCTGCTTC GCCTAATAAT                                  | TAATAAT    | AACGGTCGTC                 | GTAATATGGT                       | GGGCGGACA  |
|     |  | Hp         | Hpal                       | MscI                             | DraIII     |
| 51  | GTTTGGCGGC GGC   | ACGAAGT    | CGGC GGCACGAAGT TAACCGTTCT | TGGCCAGCCG AAAGCCGCAC            | AAAGCCGCAC |
|     | CAAACCGCCG CCG   | TGCTTCA    | CCGTGCTTCA ATTGGCAAGA      | ACCGGTCGGC                       | TTTCGGCGTG |
|     | Dralli   | :          |                            |                                  |            |
| 101 | castiges ceretifice ecsaseases aasaatisea secsaacaa    | GTTTCCG    | CCGAGCAGCG                 | AAGAATTGCA                       | GGCGAACAAA |
|     | GCTCACACTG CGACAAAGGC GGCTCGTCGC                       | CAAAGGC    | GGCTCGTCGC                 | TTCTTAACGT                       | CCGCTTGTTT |
| 151 | GCGACCCTGG TGT   | TGTGCCTGAT | TAGCGACTTT                 | TATCCGGGAG CCGTGACAGT            | CCGTGACAGT |
| •   | CGCTGGGACC ACA   | ACACGGACTA | ATCGCTGAAA                 | ATAGGCCCTC                       | GGCACTGTCA |
| 201 | GGCCTGGAAG GCAGATAGCA GCCCCGTCAA GGCGGGAGTG GAGACCACCA | GATAGCA    | GCCCCGTCAA                 | GGCGGGAGTG                       | GAGACCACCA |
|     | CCGGACCTTC CGTCTATCGT                                  | CTATCGT    | CGGGGCAGTT                 | CGGGGCAGTT CCGCCCTCAC CTCTGGTGGT | CTCTGGTGGT |

Figure 7C: functional map and sequence of module 24 comprising the synthetic CI gene segment (huCL lambda) (continued)

STGGGAGGTT TGTTTCGTTG TTGTTCATGC GCCGGTCGTC GATAGACTCG CTATCTGAGC CACCCTCCAA ACAAAGCAAC AACAAGTACG CGGCCAGCAG 251

RleAI

301

CTGACGCCTG AGCAGTGGAA GTCCCACAGA AGCTACAGCT GCCAGGTCAC SACTGCGGAC TCGTCACCNT CAGGGTGTCT TCGATGTCGA CGGTCCAGTG

StuI

CTCCGGACTA GAGGCCTGAT GCATGAGGGG AGCACCGTGG AAAAAACCGT TGCGCCGACT TTTTTGGCA ACGCGGCTGA CGTACTCCCC TCGTGGCACC

SphI

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401 AAGCATGC TTCGTACG

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Figure 7D: oligonucleotides used for synthesis of module M24 containing CA gene segment

M24: assembly PCR

M24-A: GAAGACAAGCGGATTATTATTGCCAGCAGCATTATACCACCCCGCCTGTGTTTGGCGGCG-

**GCACGAAGTTAACCGTTC** 

M24-B: CAATICTTCGCTGCTCGGCGGAAACAGCGTCACACTCGGTGCGGCTTTCGGCTGGCCAA-

GAACGGTTAACTTCGTGCCGC

M24-C: CGCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACT-

TTTATCCGGGAGCCGTGACA

M24-D: 16TTTGGAGGGTGTGGTGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGCCTTCCAG-

GCCACTGTCACGGCTCCCGG

M24-E: CCACACCCTCCAAACAAAGCAACAAGAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC-

CTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTG

M24-F: GCATGCTTATCAGGCCTCAGTCGGCGCAACGGTTTTTCCACGGTGCTCCCCTCATGCGT-

GACCTGGCAGCTGTAGCTTC

Д H Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-VK2 SapI Ц П S Ø ×

TCTTCACCCC AGAAGTGGGG AATGGCAACG TTACCGTTGC TGACCGTGAG ACTGGCACTC GCACTATTGC CGTGATAACG ATGAAACAAA TACTTTGTTT

G S 臼 Н MfeI O > 团 Ω Ω Ø × H

>

GAAAGCGGCG CTTTCGCCGC GCAATTGGTG CGTTAACCAC TTCTACTTCA GCCGACTACA AAGATGAAGT CGGCTGATGT TGTTACCAAA ACAATGGTTT

BSPEI വ Ø K Ö വ Н K Ы വ Ç Ö Д Ø > ᆸ G G

GICTGAGCTG CGCGGCCTCC GCGCCGGAGG CAGACTCGAC GGCAGCCTGC CCGTCGGACG GCAACCGGGC CGTTGGCCCG GCGCCTGGT CGCCGGACCA

Д BstXI Ø O 24 > 3 വ  $\mathbf{Z}$ Ø  $\succ$ ഗ ഗ ഥ ₽ BspEI Ŀı G

C

GGATTTACCT TTAGCAGCTA TGCGATGAGC TGGGTGCGCC AAGCCCCTGG

CCTAAATGGA AATCGTCGAT ACGCTACTCG ACCCACGCGG TTCGGGGACC

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued) H S G Ç ഗ G S വ 3 回 XhoI Ц <u>ෆ</u>

GGCAGCACCT CCGTCGTGGA GCCATCGCCG CGGTAGCGGC GCGCGATTAG CGCGCTAATC GAGTGGGTGA CTCACCCACT CTTCCCAGAG GAAGGGTCTC

NspV വ Z Ω PmlI ĸ ഗ H ſ٦, K U × > വ Ø  $\succ$ 

×

TGATAATTCG ACTATTAAGC GGTAAAGTGC CCATTTCACG GGCCGTTTTA CCGGCAAAAT ATTATGCGGA TAGCGTGAAA ATCGCACTTT TAATACGCCT

EagI 1111 Е Ω 臼 Ø 24 П വ Z Σ Ö Ц 口 H Z NspV ×

CTGCGTGCGG AAGATACGGC TTCTATGCCG GACGCACGCC TTACTTGTCG AAAAACACCC TGTATCTGCA AATGAACAGC ACATAGACGT TTTTGTGGG

Ω Σ K Ŀı G Ω G G 3 ĸ Ø  $\succ$ EagI

BSSHII

TGCGCGCGTT GGGGCGCGA TGCCTTTTAT GCGATGGATT CGTGTATTAT

CAACGGCTAT GTTGCCGATA

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-VK2 (continued) GCACATAATA ACGCGCGCAA CCCCGCCGCT ACCGAAAATA CGCTACCTAA လ BlpI Ŋ

ATTGGGGCCA AGGCACCCTG GTGACGGTTA GCTCAGCGGG TGGCGGTTCT CGAGTCGCCC ACCGCCAAGA CACTGCCAAT TAACCCGGT TCCGTGGGAC

ECORV Ω S C G r U വ G C C G ഗ G ග G C

GTTCCGATAT CAAGGCTATA GGAGCGGTGG CGGTGGTCT GGCGGTGGTG CCGCCACCAC GCCACCAAGA CCTCGCCACC GGCGGCGGTG CCGCCGCCAC

1111

Д 口 U Д > Д ß Н Д BanII လ Ø Σ ECORV >

GGCGAGCCTG CCGCTCGGAC TCACTGAGGC TGAGCCTGCC AGTGACTCCG ACTCGGACGG GTCTCGGGTG CAGAGCCCAC GCACTACTGG CGTGATGACC

C Z ഗ 田 Н ഗ O വ ഗ ĸ PstI C S ഗ K

AGCCAAAGCC TGCTGCATAG ACGACGTATC TCGGTTTCGG GACGTCTTCG CTGCAGAAGC CGAGCATTAG GCTCGTAATC

Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued) AseI CGCAGCTATT GCGTCGATAA GGTCAAAGCC Ø G SexAI ATTGGTACCT TCAAAAACCA Н KpnI Ω AACTATCTGG Н

CCAGTTTCGG TAACCATGGA AGTTTTGGT TTGATAGACC

S K . വ Д Eco01091 <u>ი</u> ഗ Ø 24 Z വ C Д AseI

GCAAAATCGC CGTTTTAGCG GTGCCAGTGG GGTCCCGGAT CCAGGGCCTA CACGGTCACC GGCAGCAACC CCGTCGTTGG AATTTATCTG TTAAATAGAC

K [z] R ß × Н Н ſτι Ω 터 G BamHI ഗ G S G

ACACCTTCGA TGTGGAAGCT TITACCCIGA AAATTAGCCG TTTAATCGGC AAATGGGACT GCTCTGGATC CGGCACCGAT GCCGTGGCTA CGAGACCTAG

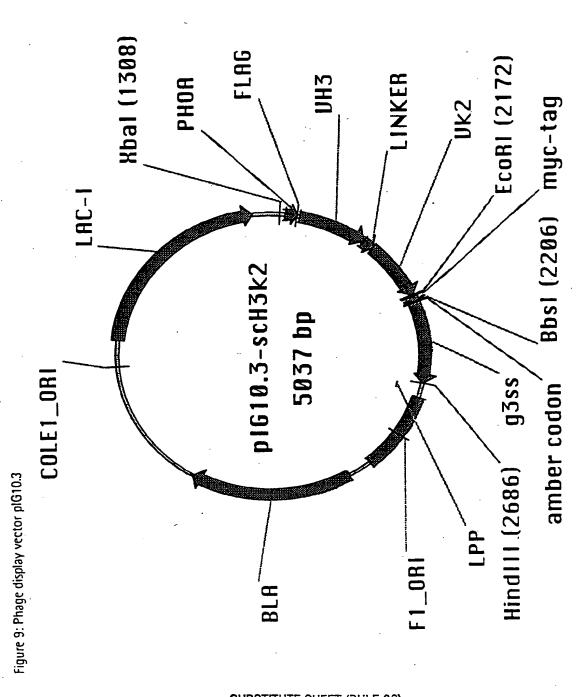
Д Д Н H 田 Ø Ø Ö  $\succ$ > G > Ω BbsI

11111

CATTATACCA CCCCGCCGAC GGGGGGGCTG GTAATATGGT TTGCCAGCAG AACGGTCGTC GCGTGTATTA CGCACATAAT GAAGACGTGG CTTCTGCACC Figure 8: sequence and restriction map of the synthetic gene encoding the consensus single-chain fragment VH3-Vk2 (continued) E Ecori ¥ 团 G Ç ہتا

R T Bsiwi

TGCATGCCTT ACGTACGGAA AACTTTAATT TTGAAATTAA CCATGCTTTC GGTACGAAAG CTTTGGCCAG GAAACCGGTC MSCI



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Figure 10: Sequence analysis of initial libraries

| 103        | <u>≥</u>     | <u>≥</u>     | <u> </u>     | <u> </u>  | ≥            | $\geq$    | <u> </u>  | <u> </u>  | ≷         | ≥        | <u>≥</u>     | <u> </u>  | <u>≷</u> |
|------------|--------------|--------------|--------------|-----------|--------------|-----------|-----------|-----------|-----------|----------|--------------|-----------|----------|
| Z01        | >            | >            | >            | >         | >            | >         | >         | >         | >-        | >-       | >            | >         | >        |
| 101        |              |              |              |           |              |           |           |           |           |          |              |           |          |
| 300 L      | , Σ          | 1            | 1            | 1         | ı            | :         | ı         | ı         | 1         | ı        | ı            | ı         | ı        |
| 000 l      | 1            | ı            | ı            | ı         | ı            | 1         | ı         | t         | 1         | 1        | ·ı           | į         | . •      |
| 200 L      | 1            | ı            | 1            | ı         | ı            | ı         | ı         | 1         | 1         |          | 1            | ı         | t        |
| 100B       | ⋖            | 1            | ı            | ı         | •            | ı         | 1         | ı         | ı         | ı        | i            | 1         | ı        |
| A001       | <b>&gt;</b>  | 1            | 1            | 1         | 1            | ı         | 1         | 1         | 1         | 1        | ı            | ı         | ı        |
| 001        | ட            | >            | エ            | I         | $\propto$    | >         | ٥         | ı         | S         | <b>Y</b> | ⋖            |           | Σ        |
| 66         | 9            | Z            | ≥            | >         | 4            | 9         | 0         | $\propto$ | Z         | S        | ⋖            | >         | ≥        |
| 86         |              | Σ            | ш            | _         | $\checkmark$ | H         | 4         | $\vdash$  | $\propto$ |          | ட            | 0         | ш        |
| <i>26</i>  | G            | $\checkmark$ | <del> </del> | ш         | نَـ          | <u></u>   | ш         | _         | Z         | G        | <b>—</b>     | ٩         | S        |
| 96         | 9            | 9            | <b>X</b>     | $\simeq$  | ட            | Z         | Z         | 4         | >         | >        | $\checkmark$ | ⋖         | 0        |
| <i>S6</i>  | ≥            | ட            | エ            | >         | ¥            | ≥         | _         | <b>—</b>  | ≥         | S        | S            | >         | Σ        |
| <b>7</b> 6 | <b>~</b>     | $\propto$    | ~            | $\propto$ | ~            | $\propto$ | $\propto$ | $\propto$ | $\simeq$  | 8        | 8            | $\propto$ | $\simeq$ |
| £6         | 4            | A            | ⋖            | ⋖         | ⋖            | ⋖         | 4         | ۷         | ⋖         | 4        | ⋖            | ⋖         | A        |
| <i>Z</i> 6 | <del>ا</del> | C            | ပ            | ၁         | ပ            | ပ         | ပ         | ပ         | ပ         | S        | S            | ပ         | $\circ$  |
| A          |              | æ            |              |           |              |           |           |           |           |          |              |           |          |

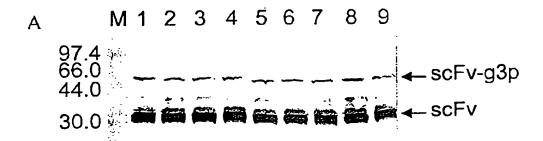
 $\Sigma \Sigma \Pi \Sigma \Sigma \Pi \Pi \Sigma \Sigma \Sigma \Sigma$ ۵ ーエト  $G + G = G \times X \times X$  $\forall \land \circlearrowleft \vdash \supset \vdash \vdash \supset \circlearrowleft$ GIQLIZKERX **」SFENE>NLYF** A >  $\geq$   $\Omega \cdot \Omega \cdot Z$  $\Sigma \sqcap R \Omega \geqslant$  $\Sigma \sqcup Z \vdash$ J Q S Y S P P S T S D T S D  $A \subseteq Q \subseteq Q \subseteq X \subseteq X$ **KKKKKKKKK** 444444444 000000000000

3333333

ပ

Figure 10: Sequence analysis of initial libraries

Figure 11: Expression analysis of initial library



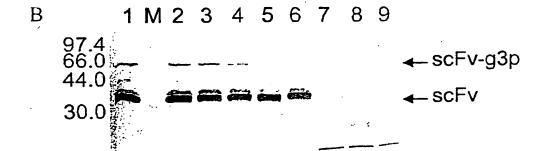


Figure 12: Increase of specificity during the panning rounds

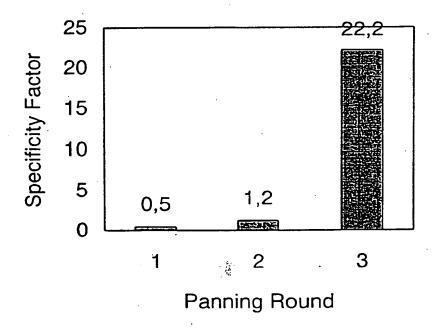
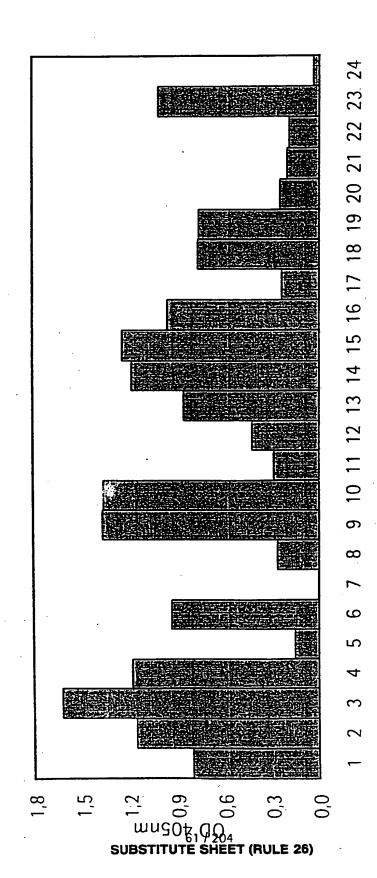
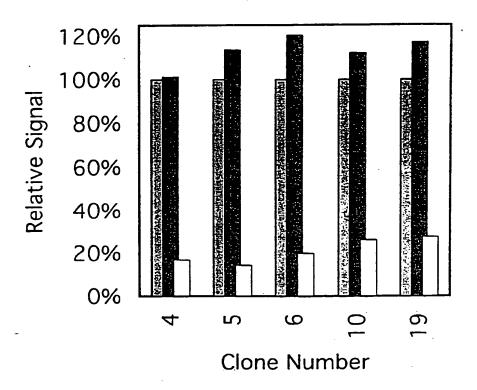


Figure 13: Phage ELISA of clones after the 3rd round of panning



Clone Number

Figure 14: Competition ELISA



- No Inhibition
- Inhibition with BSA
- ☐ Inhibition with Fluorescein

Figure 15: Sequence analysis of fluorescein binders

(100) [ KKKKKOO> X > KKK - OKK 001 Z R I R  $\overline{A}$   90 $89 \ge Q \times R - > \Sigma I \ge Q R \times I - \times R$ *1*6 ≥×∪≥×шσπ⊢ασ×>エ⊢¬ 96 ~ N Z X ~ - X X X X Z O Z X \ X **46 KKKKKKKKKKKKKK** 

Figure 16: Purification of fluorescein binding scFv fragments

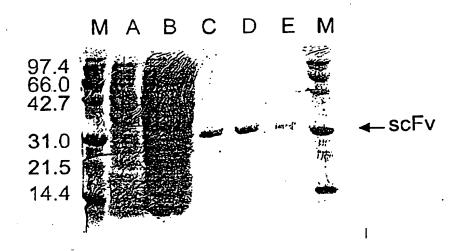
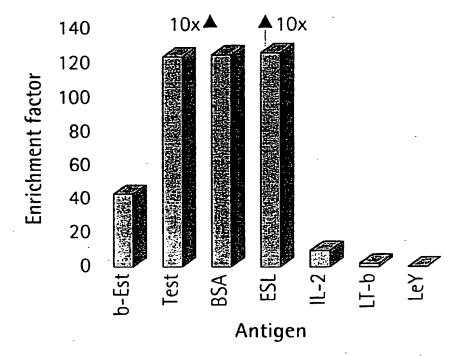


Figure 17: Enrichment factors after three rounds of panning



anti-ß-estradiol antibodies anti-ESL-1 antibodies 09-3 0.8 9.0 0.4 Jay-(muso+)do substitute sheet (rule 26) 66 / 204

Figure 18: ELISA of anti-ESL-1 and anti- $\beta\text{--estradiol}$  antibodies

Figure 19: Selectivity and cross-reactivity of HuCAL antibodies

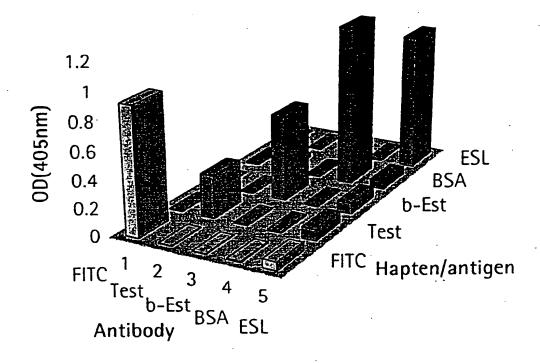


Figure 20: Sequence analysis of estradiol binders

| Frequency  | က            | &            | 7            | <del></del> | <del></del> | , <del></del> | —            | <b>-</b>     |              | 5            | 4            |              |
|------------|--------------|--------------|--------------|-------------|-------------|---------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 103        | <u>&gt;</u>  | 3            | 8            | 3           | ≥           | ≥             | ≥            | 3            | 3            | ≯            | 8            | 3            |
| 105        | >            | >            | >            | >           | >           | >-            | >-           | >            | >            | >            | >            | >            |
| 101        | ۵            | 0            |              | 0           | 0           |               | 0            | 0            | ۵            | ٥            |              | ۵            |
| 100E       | ட            | Σ            | ட            | ட           | ≥           | ≥             | ı            | Σ            | ≥            | Σ            | ≥            | ட            |
| 100D       | g            | $\checkmark$ | œ            | ட           | I           | Σ             | 1            | œ            | >            | ட            | ш            | Z            |
| J001       | $\checkmark$ | æ            | $\checkmark$ | >           | ≥           | ¥             | 1            | ×            | >            | æ            | $\checkmark$ | $\checkmark$ |
| 1008       | 8            | œ            | 9            | ш           | S           | ~             | 1            | >-           | >            | 8            | 9            | ×            |
| A001       | <b>—</b>     | Z            |              | 0           | ≥           | 工             | i            | ட            | O            | ட            | œ            | Σ            |
| 100        | V            | $\checkmark$ | ۵            |             | ட           | ∝.            | م            | ≥            | S            | $\propto$    | S            | $\propto$    |
| 66         | O            | ட            | ≥            | œ           |             | ط             | م            | エ            | ≥            | ≥            | _            | Σ            |
| 86         | ≥            | ш            | Σ            | ≥           | 9           | u             | V            | ≥            | Σ            | 0            | A            | _            |
| ۷6         | م            | ≥            | ≥            | _           | ≥           | _             | $\checkmark$ | <del> </del> | 0            | O            | _            | K            |
| 96         | œ            | O            | œ            | S           | ۵           | 0             | Σ            | $\checkmark$ | $\checkmark$ | $\checkmark$ | Σ            | Σ            |
| <i>9</i> 6 | -            | z            | $\checkmark$ | >           | ·>          | Z             | _            | <u>~</u>     | ≥            | Z            | Z            | Z            |
| <b>7</b> 6 | <u>«</u>     | œ            | 8            | œ           | <u>~</u>    | $\propto$     | æ            | œ            | œ            | œ            | œ            | $\simeq$     |
| 83         | A            | Ø            | 4            | Ø           | ⋖           | V             | Ø            | ⋖            | V            | V            | V            | ⋖            |
| <i>7</i> 6 | ں            | ن            | ں            | ပ           | ں           | ں             | ں            | ن            | ت            | ت            | ں            | َ            |

Figure 21: Sequence analysis of testosterone binders

| Frequency  | 4            | က            | 2           | <del></del>  |          | <b></b> - |
|------------|--------------|--------------|-------------|--------------|----------|-----------|
| 103        | <u> </u>     | ≥            | ≥           | ≥            | ≥        | ≥         |
| 105        | >            | >            | <b>&gt;</b> | >            | >-       | >         |
| 101        | Ω            |              | ۵           | ۵            |          | 0         |
| 100E       | ட            | ц.           | <u>ц</u>    | ட            | ட        | ட         |
| 100D       | A            | O            | O           | Σ            | ≥        | O         |
| J001       | _            | Σ            | Σ           | <b>—</b>     | ¥        | ≥         |
| 1008       | $\checkmark$ | $\checkmark$ | <u>-</u>    | $\checkmark$ | ≥        | O         |
| A001       | 8            | O            | z           | ≥            | _        | $\propto$ |
| 001        | $\checkmark$ | ≥            | œ           | ≥            | ∝.       | S         |
| 66         | ⋖            | A            | Ø           | Ø            | <u>~</u> | A         |
| 86         | O            | 工            | >           | 9            | <u> </u> | œ         |
| <b>Z</b> 6 | $\checkmark$ | ~            | ¥           | ~            | م        | $\prec$   |
| 96         | _            | Z            | >           | ¥            | <b>×</b> | œ         |
| <i>9</i> 6 | >            | >            | >-          | >            | .œ       | >-        |
| <b>7</b> 6 | æ            | æ            | œ           | œ            | <u>~</u> | 8         |
| 83         | ×            | A            | A           | A            | A        | V         |
| 76         | <del>ا</del> | ں            | ں           | ں            | ں        | ں         |

Figure 22: Sequence analysis of lymphotoxin-B binders

Frequency 103 333333 105 101 300 €  $\sum \sum i r \sum i r$ 000 l I G Q S > V S S J001 H H O H Y 1008 H A001 001 66 86 **Z**6 96  $\kappa \geqslant \land \circ \neg \geqslant \circ \geqslant$ 96 ロハスストロ **7**6 **EEEEEEE 4444444** 63 76

Figure 23: Sequence analysis of ESL-1 binders

103 33333333333 105 101 300 €  $\Sigma \Sigma \Sigma \Sigma \bot \bot \Sigma \bot$ 000 L 100Ca J001 100B  $4 \leq 2 \leq 1$ A001 001 66 86 **Z**6  $TZ \succ \bot \lor S \succ$ 96 96 **KKKKKKKKKK 7**6 4444444444 63 

Figure 24: Sequence analysis of BSA binders

76

## 103 3333 105 101 100E $\Sigma \sqcap \Sigma \Sigma \Sigma \sqcap$ J001 > x x Q > J001 100B A001 001 66 86 **Z**6 96 96 **7**6 63 AAAAAA

#S‡∥

mpA \male p/o+lox'
Xbal BgIII @ lox site lox site ColEI Ext2 origin p15A module AatIII Jac p/o cat phoA pCAL system Nhel fl ori Fsel BsrGI lox' site ss IIIg I Pacl Ipp-Terminator (His, myc) Hind 1 tails domains BESSEA BE module IMPfunctions (IL2) lacI effector SUBSTITUTE SHEET (RULE 26)

Figure 25: modular pCAL vector system

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Figure 25a: List of unique restriction sites used in or suitable for HuCAL genes or pCAL vectors

| unique restriction site | Isoschizomers                     |
|-------------------------|-----------------------------------|
| Aatii                   | 1                                 |
| AfIII                   | Bfrl, BspTl, Bst981               |
| Ascl                    | 1                                 |
| Asel                    | Vspl, Asnl, PshBl                 |
| BamHI                   | Bstl                              |
| Bbel                    | Ehel, Kasl, Narl                  |
| Bbsl                    | BpuAl, Bpil                       |
| BgIII                   | - /                               |
| Blpl                    | Bpu11021,Cell1, Blp1              |
| BsaBl                   | Mami, Bsh1365i, BsrBRi            |
| BsiWl                   | Pfl23ll, Spll, Sunl               |
| BspEl                   | AccIII, BseAI, BsiMI, Kpn2I, Mrol |
| BsrGl                   | Bsp1407l, SspBl                   |
| BssHII                  | Paul                              |
| BstEll                  | BstPl, Eco91l, Eco0651            |
| BstXI                   |                                   |
| Bsu36l                  | Aocl, Cvnl, Eco811                |
| Dralll                  |                                   |
| DsmAl                   |                                   |
| Eagl                    | BstZl, EclXl, Eco52l, Xmalll      |
| Eco57l                  | .                                 |
| Eco0109l                | Drall                             |
| EcoRI                   |                                   |
| EcoRV                   | Eco32l                            |
| Fsel                    | <u> </u>                          |
| HindIII                 | <u> </u>                          |
| Hpal                    |                                   |
| Kpnl                    | Acc65l, Asp718l                   |
| Miul                    | 1.                                |
| Mscl                    | Ball, MluNl                       |

WO 97/08320 PCT/EP96/03647

Figure 25a: List of unique restriction sites used in or suitable for HuCAL genes or pCAL vectors

| unique restriction site | Isoschizomers                      |
|-------------------------|------------------------------------|
| Muni                    | Mfel                               |
| Nhel                    |                                    |
| Nsil                    | Ppu10l, EcoT22l, Mph1103l          |
| NspV                    | Bsp1191, BstBl, Csp451, Lsp1, Sful |
| Pacl                    |                                    |
| Pmel                    |                                    |
| PmII                    | BbrPl, Eco72I, PmaCl               |
| Psp5II                  | PpuMI                              |
| Pstl                    | 1                                  |
| Rsrll                   | (Rsril), Cpol, Cspl                |
| SanDI                   |                                    |
| Sapl                    |                                    |
| SexAl                   |                                    |
| Spel                    |                                    |
| Sfil                    |                                    |
| Sphl                    | Bbul, Pael, Nspl                   |
| Stul                    | Aatl, Eco147l                      |
| Styl                    | Eco130l, EcoT14l                   |
| Xbal                    | BspLU11II                          |
| Xhol                    | PaeR7I                             |
| Xmal                    | Aval, Smal, Cfr9l, PspAl           |

| WO 97/08320             | )                   |                              |  |                                | PCT/EP96/03647  |
|-------------------------|---------------------|------------------------------|--|--------------------------------|---|
| reference               | Skerra et al (1991) | Bio/Technology 9,<br>273-278 | Hoess et al. (1986)<br>Nucleic Acids Res.<br>2287-2300 | see M2                         | Ge et al., (1994) Expressing antibodies in E. coli. In: Antibody engineering: A practical approach. IRL Press, New York, pp 229-266 |
| template                |                     | vector<br>pASK30             | (synthetic)  | (synthetic)                    | vector<br>plG10   |
| sites to be<br>inserted |                     | Aatll                        | lox, BgIII   | lox', Sphl                     | none  |
| sites to be<br>removed  |                     | 2x Vspl<br>(Asel)            | 2x Vspl<br>(Asel)                                      | none                           | Sphl,<br>BamHl  |
| functional element      |                     | lac<br>promotor/operator     | Cre/lox<br>recombination site                          | Cre/lox'<br>recombination site | glllp of filamentous<br>phage with N-<br>terminal<br>myctail/amber<br>codon   |
| module/flan-king func   | sites               | Aatil-lacp/o-<br>Xbal        | BgIII-lox-<br>Aatll                                    | Xbal-lox'-<br>Sphl             | EcoRI-<br>gIlllong-<br>HindIII  |
| No                      |                     | M                            | M2   | M3                             | I-7M  |

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| r modules    |
|--------------|
| pCAL vector  |
| ist of       |
| Figure 26: 1 |

| 1 | WO 97/08320   |  |                               |                        |                              | PCT/E                                     | P96/03647                                 |
|---|---|--|-------------------------------|------------------------|------------------------------|---|---|
|   | see M7-I  | see M7-I   | see M3                        | see M1                 | see M1                       | see M1                                    | see M1                                    |
|   | vector<br>plG10   | vector<br>plG10  | (synthetic)                   | Pacl, Fsel (synthetic) | pASK30                       | pASK30                                    | pASK30                                    |
|   |   |  | lox                           | Paci, Fsei             | Pacl, Fsel,<br>BsrGl         | BsrGl, Nhel                               | BsrGl, Nhel                               |
|   | Sphl  | Sphl, Bbsl   | none                          | none                   | Vspl,<br>Eco571,<br>BssSI    | Dralli<br>(Banll not<br>removed)          | DrallI,<br>BanlI                          |
|   | truncated gillp of<br>filamentous phage<br>with N-terminal Gly-<br>Ser linker | truncated gillp of filamentous phage with N-terminal myctail/amber codon | Cre/lox<br>recombination site | lpp-terminator         | beta-lactamase/bla<br>(ampR) | origin of single-<br>stranded replication | origin of single-<br>stranded replication |
|   | EcoRI-gIIIss-<br>HindIII  | M7-III EcoRI-gIIIss-<br>HindIII  | Sphl-lox-<br>HindIII          | HindIII-Ipp-<br>Pacl   | M10- Pacl/Fsel-bla-          | M11- BsrGI-f1 ori-                        | BsrGI-f1 ori-<br>Nhel                     |
|   | M7-11   | M7-III   | M8                            | M9-II                  | M10-                         | M11-                                      | M11-                                      |

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Figure 26: list of pCAL vector modules

PCT/EP96/03647

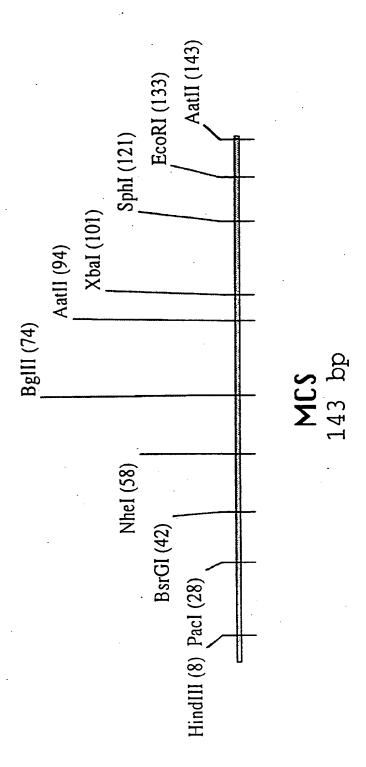
| WO 97/0832   | 0                             |  |  |                                  | PCT/EP96  |
|--|-------------------------------|--|--|----------------------------------|---|
| Rose, R.E. (1988)<br>Nucleic Acids Res.<br>16, 355 | see M3                        | Yanisch-Peron, C.<br>(1985) Gene<br>33,103-119 | Cardoso, M. & Schwarz, S. (1992)<br>J. Appl.<br>Bacteriol. 72, 289-293 | see M1                           | Knappik, A &<br>Plückthun, A.<br>(1994)<br>BioTechniques 17,<br>754-761 |
| Nhel, Bglll pACYC184                               | (synthetic)                   | pUC19  | pACYC184   | (synthetic)                      | (synthetic)   |
| Nhel, Bglll  | BgIII, lox,<br>Xmnl           | BgIII, Nhel                                    |  |                                  | ·   |
| BssSI, VspI,<br>NspV                               | none                          | Eco57l<br>(BssSl not<br>removed)               | BspEI, MscI,<br>Styl/Ncol  | (synthetic)                      | (synthetic)   |
| origin of double-<br>stranded replication          | Cre/lox<br>recombination site | origin of double-<br>stranded replication      | chloramphenicol-<br>acetyltransferase/<br>cat (camR)                   | signal sequence of phosphatase A | signal sequence of<br>phosphatase A +<br>FLAG detection tag             |
| Nhel-p15A-<br>BgIII                                | BgIII-lox-<br>BgIII           | BgIII-ColEI-<br>Nhel                           | Aatll-cat-<br>BgIII  | Xbal-phoA-<br>EcoRl              | Xbal-phoA-<br>FLAG-EcoRI  |
| M12  | M13                           | M14-<br>Ext2                                   | M17  | M19                              | M20   |

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| igure 2   |
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| WO 97/08320  | )  |   |
|--|--|---|
| Lee et al. (1983)<br>Infect. Immunol.<br>264-268             | see M1   | Lindner et al.,<br>(1992) Methods: a<br>companion to<br>methods in<br>enzymology 4, 41-<br>56 |
| (synthetic)  | pASK30   | (synthetic)   |
|  |  |   |
| (synthetic)  | BstXI,<br>MluI,BbsI,<br>BanII,<br>BstEII,<br>HpaI, BbeI,<br>VspI | (synthetic)   |
| heat-stable<br>enterotoxin II signal (synthetic)<br>sequence | lac-repressor  | poly-histidine tail   |
| Xbal-stll-<br>Sapl   | Afill-laci-<br>Nhel  | EcoRI-Histail-<br>HindIII   |
| M21  | M41  | M42   |

Figure 27: functional map and sequence of MCS module



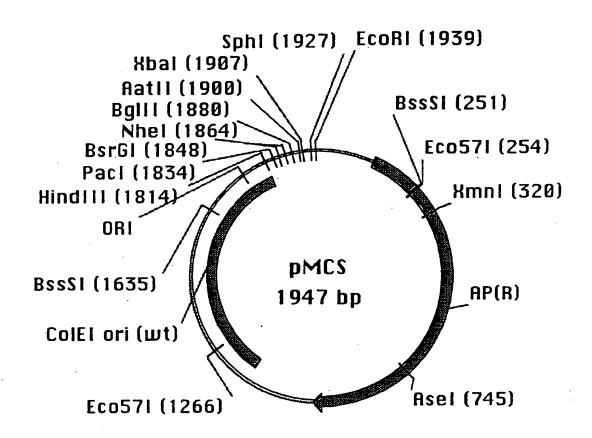
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| (continued)               |
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| module                    |
| of MCS                    |
| ial map and sequence of P |
| pue der                   |
| functional n              |
| Figure 27:                |

| <b>1</b> | HindIII                                 | II                    | PacI                                    | BsrGI   |
|----------|---|-----------------------|---|---|
|          | ? | ~ .                   | 2 | 1             |
| ᡤ        | ACATGTAAGC                              | ACATGTAAGC TTCCCCCCCC | ACATGTAAGC TTCCCCCCC CCTTAATTAA         | CCCCCCCCC TGTACACCCC                                |
|          |   |                       |   |   |
|          | NheI                                    |                       | BglII                                   | Aatll Xbal  |
|          | 1 | <b>?</b>              | ~ ~ ~ ~ ~                               | *             |
| 51       | CCCCCCGCTA                              | ವಿವಿವಿವಿವಿವಿವಿವಿ      | CCAGATCTCC                              | CCCCCCCCTA GCCCCCCCC CCAGATCTCC CCCCCCCGA CGTCCCCCT |
| -        | GGGGGGCGAT                              | 555555555             | GGGGGCGAT CGGGGGGGG GGTCTAGAGG          | GGGGGGGCT GCAGGGGGGA                                |
|          |   |                       |   |   |
|          | XbaI                                    | SphI                  |   | EcoRI AatII   |
|          | 2 2 2 2 2 2                             | 2 2 2 2 2 2           | ?                                       | ***********   |
| 101      | CTAGACCCCC                              | CCCCCGCATG            | 222222222                               | CTAGACCCCC CCCCCCCTG CCCCCCCC CGAATTCGAC GTC        |
|          | GATCTGGGGG                              | GGGGCGTAC             | 9999999999                              | GGGGGCGTAC GGGGGGGG GCTTAAGCTG CAG                  |

Figure 28: functional map and sequence of pMCS cloning vector



| Figure 28: functional map and sequence of pMCS cloning vector (continued) |  | 777                  |
|---|--|----------------------|
| Figure 28: functional map and sequence of pMCS cloning vector             | (continued)  |                      |
|   | Figure 28: functional map and sequence of pMCS cloning vector (c | *CCCCEEEE C*CCCECT*C |

| TTGTTTTTT                        | AACAAATAAA          |
|----------------------------------|---------------------|
| AATGTGCGCG GAACCCCTAT TTGTTTATTT | ACACGCGC CTTGGGGATA |
| AATGTGCGCG                       | $\Gamma$            |
| TTTTCGGGGA 1                     | AAAAGCCCCT          |
| CAGGTGGCAC                       | GTCCACCGTG          |
| <del></del> 1                    |                     |

- AACCCTGATA TTGGGACTAT ATGAGACAAT TACTCTGTTA CATAGGCGAG GTATCCGCTC TAAGTTTATA ATTCAAATAT AAGATTTATG **LTCTAAATAC**
- CAACATTTCC GTTGTAAAGG ATACTCATAA TATGAGTATT TTTCCTTCTC AAAGGAAGAG ATTATAACTT TAATATTGAA TTACGAAGTT AATGCTTCAA 101
- ACAAAAACGA TGTTTTGCT AAACGGAAGG TTTGCCTTCC AAACGCCGTA TTTGCGGCAT ATAAGGGAAA TATTCCCTTT GTGTCGCCCT 151

CACAGCGGGA

TCAACCCACG AGTTGGGTGC BssSI CGACTTCTAG GCTGAAGATC Eco57I TCATTTTCTA AGTAAAAGAT CGCTGGTGAA GCGACCACTT CACCCAGAAA GTGGGTCTTT 201

ATCCTTGAGA TAGGAACTCT CAGCGGTAAG GTCGCCATTC TGGATCTCAA ACCTAGAGTT TACATCGAAC ATGTAGCTTG ACGAGTGGGT TGCTCACCCA 251

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CCCCTAGTAC

CGTGTTGTAC

GGCGAAAAAA

TTCCTCGATT

GCCTCCTGGC

Figure 28: functional map and sequence of pMCS cloning vector (continued)

XmnI

| GCCC CGAAGAACGI IIICCAAIGA IGAGCACIII IAAAGIICIG<br>CGGG GCTTCTTGCA AAAGGTTACT ACTCGTGAAA ATTTCAAGAC |
|--|
| GCTTCTTGCA AAAG  |

TCACCAGTCA AGTGGTCAGT

GGTTGAGTAC

AGAATGACTT TCTTACTGAA

CACTATTCTC GTGATAAGAG

TCGCCGCATA

401

| •   |  |   |
|---|--|---|
| ATGCAGTGCT<br>TACGTCACGA                        | TGACAACGAT<br>ACTGTTGCTA                         | GGGGATCATG                                      |
| GCA TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT | NCCA TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT | CCG AAGGAGCTAA CCGCTTTTTT GCACAACATG GGGGATCATG |
| GGCATGACAG<br>CCGTACTGTC                        | CACTGCGGCC<br>GTGACGCCGG                         | CCGCTTTTT                                       |
| TCTTACGGAT<br>AGAATGCCTA                        | TGAGTGATAA<br>ACTCACTATT                         | AAGGAGCTAA                                      |
| CAGAAAAGCA<br>GTCTTTTCGT                        | GCCATAACCA<br>CGGTATTGGT                         | CGGAGGACCG                                      |
| 451   | 501  | 551   |

| CATACCAAAC   | GTATGGTTTG                         |
|--|------------------------------------|
| TGAATGAAGC   | A ACTAGCAACC CTTGGCCTCG ACTTACTTCG |
| GAACCGGAGC   | CTTGGCCTCG                         |
| TGATCGTTGG   | ACTAGCAACC                         |
| TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC CATACCAAAC | ATTGAGCGGA                         |
| 601  |                                    |

GACGAGCGTG ACACCACGAT GCCTGTAGCA ATGGCAACAA CGTTGCGCAA 651

CTGCTCGCAC TGTGGTGCTA CGGACATCGT TACCGTTGTT GCAACGCGTT Figure 28: functional map and sequence of pMCS cloning vector (continued)

| ,    | Ę                                |                          |                          |                          | Ŕ                        |
|------|----------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 701  | ACTATTAACT<br>TGATAATTGA         | GGCGAACTAC<br>CCGCTTGATG | TTACTCTAGC<br>AATGAGATCG | TTC                      | TTCCCGGCAA               |
| 751  | ACTGGATGGA<br>TGACCTACCT         | GGCGGATAAA<br>CCGCCTATTT | GTTGCAGGAC<br>CAACGTCCTG | CACT<br>GTGA             | CACTTCTGCG<br>GTGAAGACGC |
| 801  | CCGCCTGGCT                       | GGTTTATTGC<br>CCAAATAACG | TGATAAATCT<br>ACTATTTAGA | GGAGC                    | GGAGCCGGTG<br>CCTCGGCCAC |
| 851  | TCGCGGTATC AGCGCCATAG            | ATTGCAGCAC<br>TAACGTCGTG | TGGGGCCAGA<br>ACCCCGGTCT | TGGTA                    | TGGTAAGCCC<br>ACCATTCGGG |
| 901  | TAGTTATCTA                       | CACGACGGG<br>GTGCTGCCCC  | AGTCAGGCAA<br>TCAGTCCGTT | CTATGGATGA<br>GATACCTACT | SATGA                    |
| 951  | CAGATCGCTG                       | AGATAGGTGC<br>TCTATCCACG | CTCACTGATT<br>GAGTGACTAA | AAGCATTGGT<br>TTCGTAACCA | rtggt<br>Aacca           |
| 1001 | CCAAGTTTAC TCATATATAC TTTAGATTGA | TCATATATAC<br>AGTATATATG | TTTAGATTGA               | TTTAAAACTT               | AACTT<br>PTGA 2          |

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TGGTCACCGA

ATTAGGACAA

GAGCGAGACG

CGGATGTATG

CTGTAGCACC

1351

GACATCGTGG

TTCAAGAACT AAGTTCTTGA

TCCGGTGGTG

CTTCTAGTGT AGCCGTAGTT AGGCCACCAC

TCGGCATCAA

GAAGATCACA

AAATACTGTC TTTATGACAG

1301

GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT

Figure 28: functional map and sequence of pMCS cloning vector (continued)

| GACCAAAATC<br>CTGGTTTTAG   | TAGAAAAGAT<br>ATCTTTTCTA                       | TGCTGCTTGC<br>ACGACGAACG                       | GGATCAAGAG<br>CCTAGTTCTC  | CGCAGATACC<br>GCGTCTATGG                                 |
|--|--|--|---|--|
| ATCCTTTTTG ATAATCTCAT GACCAAAATC<br>TAGGAAAAAC TATTAGAGTA CTGGTTTTAG | TCAGACCCCG<br>AGTCTGGGGC                       | GCGCGTAATC<br>CGCGCATTAG                       | CCAGCGGTGG TTTGTTTGCC GGATCAAGAGGGGTCGCCACC AAACAAACGG CCTAGTTCTC | GGTAACTGGC TTCAGCAGAG<br>CCATTGACCG AAGTCGTCTC<br>Eco57I |
| ATCCTTTTTG<br>TAGGAAAAAC   | CCACTGAGCG<br>GGTGACTCGC                       | CTTTTTTTCT GCGCGTAATC<br>GAAAAAAAGA CGCGCATTAG | CCAGCGGTGG<br>GGTCGCCACC  | GGTAACTGGC TTCAGCAGAG<br>CCATTGACCG AAGTCGTCTC<br>Eco57I |
| CTAGGTGAAG<br>GATCCACTTC   | AGTTTTCGTT<br>TCAAAAGCAA                       | TCTTGAGATC<br>AGAACTCTAG                       | AAACAAAAA ACCACCGCTA<br>TTTGTTTTT TGGTGGCGAT                      | TTTTTCCGAA<br>AAAAAGGCTT                                 |
| TTAAAAGGAT<br>AATTTTCCTA   | CCTTAACGTG AGTTTTCGTT<br>GGAATTGCAC TCAAAAGCAA | CAAAGGATCT<br>GTTTCCTAGA                       | AAACAAAAA<br>TTTGTTTTTT   | CTACCAACTC<br>GATGGTTGAG                                 |
| 1051   | 1101   | 1151   | 1201  | 1251   |
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AAACGCCAGC AACGCGGCCT TTTTACGGTT CCTGGCCTTT TGCTGGCCTT

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Figure 28: functional map and sequence of pMCS cloning vector (continued)

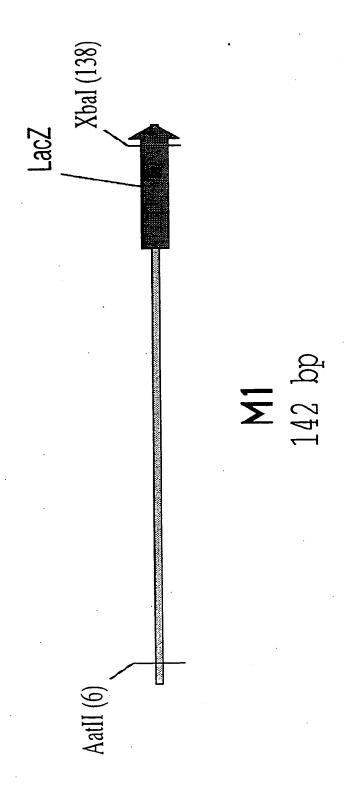
| /O 97/0    |                          |                          |                          |                                   |                          | PC1/EP9                  |
|------------|--------------------------|--------------------------|--------------------------|-----------------------------------|--------------------------|--------------------------|
| GTTCTGCTAT | TCGTGCACAC<br>AGCACGTGTG | CCTACAGCGT<br>GGATGTCGCA | CGGACAGGTA<br>GCCTGTCCAT | GAGCTTCCAG<br>CTCGAAGGTC          | CCACCTCTGA               | GCCTATGGĀA<br>CGGATACCTT |
| CCCAACCTGA | AACGGGGGGT<br>TTGCCCCCCA | AACTGAGATA<br>TTGACTCTAT | GGGAGAAAGG<br>CCCTCTTTCC | GCGCACGAGG<br>CGCGTGCTCC<br>BSSSI | TCGGGTTTCG               | GGGGGGCGGA               |
| CACAGAATGG | GGTCGGGCTG<br>CCAGCCCGAC | ACCTACACCG<br>TGGATGTGGC | GCTTCCCGAA<br>CGAAGGGCTT | GAACAGGAGA<br>CTTGTCCTCT          | TATAGTCCTG<br>ATATCAGGAC | ATGCTCGTCA<br>TACGAGCAGT |
| CGCIAIICAG | AAGGCGCAGC<br>TTCCGCGTCG | GGAGCGAACG<br>CCTCGCTTGC | AAAGCGCCAC<br>TTTCGCGGTG | GGCAGGGTCG<br>CCGTCCCAGC          | CTGGTATCTT<br>GACCATAGAA | GATTTTTGTG<br>CTAAAAACAC |
| CGACGGTCAC | GTTACCGGAT<br>CAATGGCCTA | AGCCCAGCTT<br>TCGGGTCGAA | GAGCTATGAG<br>CTCGATACTC | TCCGGTAAGC<br>AGGCCATTCG          | GGGGAAACGC<br>CCCCTTTGCG | CTTGAGCGTC<br>GAACTCGCAG |
|            | 1451                     | 1501                     | 1551                     | 1601                              | 1651                     | 1701                     |
|            |                          |                          | SUBSTITI                 | JTE SHEET (RULE 2                 | 6)                       |                          |

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TTTGCGGTCG TTGCGCCGGA AAAATGCCAA GGACCGGAAA ACGACCGGAA Figure 28: functional map and sequence of pMCS cloning vector (continued)

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Figure 29: functional map and sequence of pCAL module M1



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Figure 29: functional map and sequence of pCAL module M1

AatII

GGCTTTACAC CCGAAATGTG TCCGTGGGGT AGGCACCCCA GAGTGAGTAA CTCACTCATT ACACTCAATC TGTGAGTTAG CTGCAGAATT GACGTCTTAA

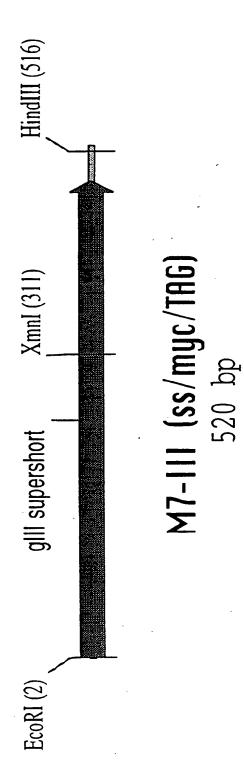
GATAACAATT CTATTGTTAA TAACACTCGC ATTGTGAGCG CAACACACCT GTTGTGTGGA GCCGAGCATA CGGCTCGTAT AAATACGAAG TTTATGCTTC 51

XbaI

GA CT CGAATTTCTA GCTTAAAGAT AACAGCTATG ACCATGATTA TTGTCGATAC TGGTACTAAT TCACACAGGA AGTGTGTCCT 101

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Figure 30: functional map and sequence of pCAL module M7-II



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| (continued)                              |
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| M7-II                                    |
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| f pCAL                                   |
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| ional map and sequence of pCAL module M7 |
| and                                      |
| map                                      |
| 30: functional                           |
| 30:                                      |
| Figure 3                                 |

|       |                  | GTGGTGG   |
|-------|------------------|---|
|       | ٠                | GAATICGAGC AGAAGCIGAT CICIGAGGAG GAICIGIAGG GIGGIGC |
|       |                  | CTCTGAGGAG  |
|       |                  | AGAAGCTGAT  |
| EcoRI | ?<br>?<br>?<br>? | GAATTCGAGC  |
|       |                  | $\vdash$  |
|       |                  |   |

AATAAGGGGG TTATTCCCCC CTAGACATCC CACCACCGAG CCGTTTGCGA GGCAAACGCT TCTTCGACTA GAGACTCCTC TACTTTTCTA ATGAAAAGAT CTAAAACTAA GATTTTGATT CTTAAGCTCG ACCAAGGCCA TGGTTCCGGT 51

GCGATTTCCG CGCTAAAGGC ATGTCAGACT TACAGTCTGA CTTTTGCGCG GAAAACGCGC AAATGCCGAT TTTACGGCTA CTATGACCGA SATACTGGCT 101

ATGGTTTCAT TACCAAAGTA GCTGCTATCG CGACGATAGC ACTAATGCCA TGATTACGGT GACAGCGATG CTGTCGCTAC TTTGAACTAA AAACTTGATT

GGTGATTTTG CCACTAAAAC TGGTGCTACT ACCACGATGA CTAATGGTAA GATTACCATT TCCGGCCTTG AGGCCGGAAC ACCACTGCAA TGGTGACGTT

TAATTCACCT ATTAAGTGGA GTGACGGTGA CACTGCCACT GCTCAAGTCG CGAGTTCAGC TTCCCAAATG AAGGGTTTAC CTGGCTCTAA GACCGAGATT 251

## XmnI

AATCGGTTGA TTAGCCAACT TCCCTCCCTC AGGGAGGAG ATATTTACCT TATAAATGGA ATTTCCGTCA TAAAGGCAGT TTAATGAATA AATTACTTAT 301

SUBSTITUTE SHEET (RULE 26) 92 / 204

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201

THTTCTATTG

Figure 30: functional map and sequence of pCAL module M7-II (continued)

| ATGTCGCCCT TTTGTCTTTG GCGCTGGTAA ACCATATGAA TTTTCTATTG |
|--|
| TCGCCCT TTTGTCTTTG GCGCTGGTAA                          |
| TCGCCCT TTTGTCTTTG                                     |
| TCGCCCT  |
| ATG  |
| 351  |

TACAGCGGGA AAALAG

TCTTTGCGTT TCTTTTATAT AGAAAATATA AGAAACGCAA TTCCGTGGTG AAGGCACCAC TTATTTGAAT AATAAACTTA TAACACTGTT ATTGTGACAA 401

ATGACGCATT TACTGCGTAA TAAAAGATGC AAACGATTGT TTTGCTAACA TTATGTATGT ATTTTCTACG CAACGGTGGA AATACATACA GTTGCCACCT

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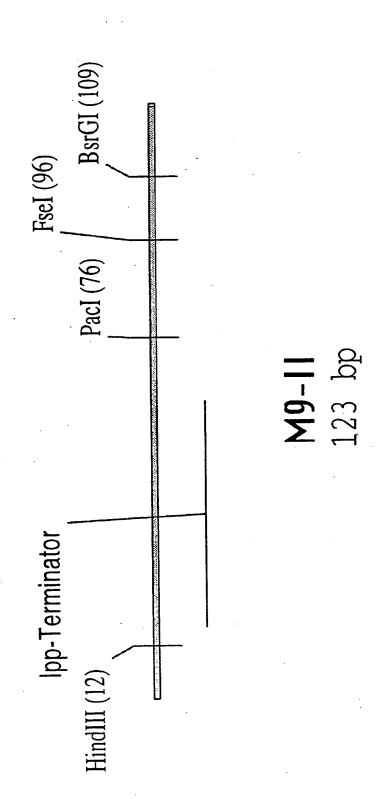
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ACTATTCGAA TGATAAGCTT ATTCCTCAGA TAAGGAGTCT

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| Il (continued)                           |
|--|
| e M9-11 (c                               |
| al map and sequence of pCAL module M9-II |
| sequence of                              |
| map and                                  |
| 1: functional                            |
|  |
| Figure 3                                 |

HindIII

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TCTAACACGC AGATTGTGCG AAAATGGCGC TTTTACCGCG TGTGAAGTGA ACACTTCACT TTCGAACTGG AAGCTTGACC 9999999999 c

PacI

FseI

CGGCCGGACC GCCGGCCTGG c9999999999 TTAATTAAAG AATTAATTTC ACAGACGGCA TGTCTGCCGT TGTAAAAAA ACATTTTTT

51

BsrGI

101 GGGGGGTGT ACAGGGGGG GGG CCCCCCCACA TGTCCCCCCC CCC

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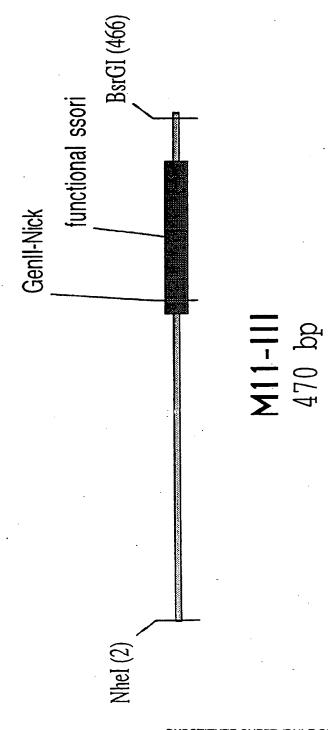


Figure 32: functional map and sequence of pCAL module M11-III

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TATICITITG ATTIATAAGG GATTITGCCG ATTICGGCCT ATTGGTTAAA

351

Figure 32: functional map and sequence of pCAL module M11-III (continued)

NheI	

	$\vdash$	GCTAGCACGC CGATCGTGCG	GCCCTGTAGC	GGCGCATTAA CCGCGTAATT	၁၁၁၅၁၁၅၁၅၁	TGTGGTGGTT ACACCACCAA
	51	ACGCGCAGCG TGCGCGTCGC	TGACCGCTAC ACTGGCGATG	ACTTGCCAGC TGAACGGTCG	GCCCTAGCGC CGGGATCGCG	CCGCTCCTTT GGCGAGGAAA
	101	CGCTTTCTTC GCGAAAGAAG	CCTTCCTTTC GGAAGGAAAG	TCGCCACGTT AGCGGTGCAA	CGCCGGCTTT GCGGCCGAAA	CCCCGTCAAG GGGGCAGTTC
	151	CTCTAAATCG GAGATTTAGC	GGGCATCCCT CCCGTAGGGA	TTAGGGTTCC AATCCCAAGG	GATTTAGTGC CTAAATCACG	TTTACGGCAC AAATGCCGTG
,	201	CTCGACCCCA GAGCTGGGGT	AAAAACTTGA TTTTTGAACT	TTAGGGTGAT AATCCCACTA	GGTTCTCGTA CCAAGAGCAT	GTGGCCCATC CACCCGGTAG
	251	GCCCTGATAG CGGGACTATC	ACGGTTTTTC TGCCAAAAAG	GCCCTTTGAC	GTTGGAGTCC CAACCTCAGG	ACGTTCTTTA TGCAAGAAAT
	301	ATAGTGGACT TATCACCTGA	CTTGTTCCAA GAACAAGGTT	ACTGGAACAA TGACCTTGTT	CACTCAACCC GTGAGTTGGG	TATCTCGGTC ATAGAGCCAG

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TAACCAATTT	
TAAATATTCC CTAAAACGGC TAAAGCCGGA TA	
CTAAAACGGC	
TAAATATTCC	
ATAAGAAAAC	

AAAATATTAA TTTTATAATT GAATTTTAAC CTTAAAATTG TTAAATTGCG AATTTAACGC ATTTAACAAA TAAATTGTTT AAATGAGCTG TTTACTCGAC 401

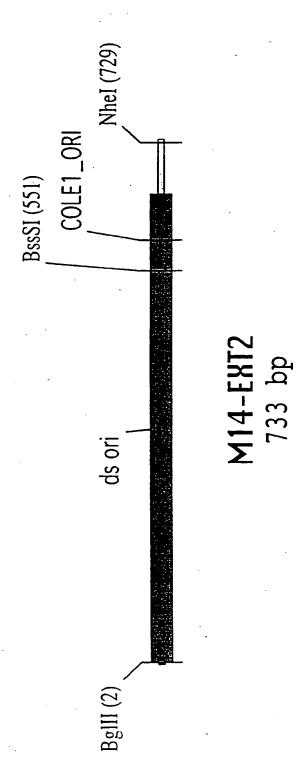
BsrGI

CGTTTACAAT TTCATGTACA GCAAATGTTA AAGTACATGT

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of nCAl module M14-Ext2 (continued)

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Figure 33: functional map and sequence of pear industry from the table	
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Figure	

TGAGCGTCAG	TTTTCTGCGC AAAAGACGCG
AGATCTGACC AAAATCCCTT AACGTGAGTT TTCGTTCGT TGAGCGTCAG	ACCCCGTAGA AAAGATCAAA GGATCTTCTT GAGATCCTTT TTTTCTGCGC
TCTAGACTGG TTTTAGGGAA TTGCACTCAA AAGCAAGGTG ACTCGCAGTC	TGGGGCATCT TTTCTAGTTT CCTAGAAGAA CTCTAGGAAA AAAAGACGCG
AACGTGAGTT	GGATCTTCTT
TTGCACTCAA	CCTAGAAGAA
AAAATCCCTT	AAAGATCAAA
TTTTAGGGAA	TTTCTAGTTT
AGATCTGACC	ACCCCGTAGA
TCTAGACTGG	TGGGGCATCT
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SGTTTG CCAAAC	SCTACA
CGGTC	ACTG( TGAC(
TCTGCT GCTTGCAAAC AAAAAACCA CCGCTACCAG CGGTGGTTTG	'TGCCGGAT CAAGAGCTAC CAACTCTTTT TCCGAAGGTA ACTGGCTACA
AGACGA CGAACGTTTG TTTTTTGGT GGCGATGGTC GCCACCAAAC	AACGGCCTA GTTCTCGATG GTTGAGAAAA AGGCTTCCAT TGACCGATGT
AAAAAACCA	CAACTCTTTT
TTTTTTGGT	GTTGAGAAAA
GCTTGCAAAC	CAAGAGCTAC
CGAACGTTTG	GTTCTCGATG
GTAATCTGCT GCTTGCAAAC AAAAAAACCA CCGCTACCAG CGGTGGTTTG	TTTGCCGGAT
CATTAGACGA CGAACGTTTG TTTTTTGGT GGCGATGGTC GCCACCAAAC	AAACGGCCTA
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GTAGTTAGGC	CATCAATCCG		CTCTGCTAAT
CGCA GATACCAAAT ACTGTTCTTC TAGTGTAGCC GTAGTTAGGC	GCGT CTATGGTTTA TGACAAGAAG ATCACATCGG CATCAATCCG		TTCA AGAACTCTGT AGCACCGCCT ACATACCTCG CTCTGCTAAT
ACTGTTCTTC	TGACAAGAAG		AGCACCGCCT
GATACCAAAT	CTATGGTTTA	-	AGAACTCTGT
GCAGAGCGCA	CGTCTCGCGT		CACCACTTCA
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GAGACGATTA	CTTACCGGGT	GAATGGCCCA
AAGT TCTTGAGACA TCGTGGCGGA TGTATGGAGC GAGACGATTA	ACCA GIGGCIGCIG CCAGIGGCGA TAAGICGIGI CITACCGGGI	TGGT CACCGACGAC GGTCACCGCT ATTCAGCACA GAATGGCCCA
TCGTGGCGGA	CCAGTGGCGA	GGTCACCGCT
TCTTGAGACA	GTGGCTGCTG	CACCGACGAC
GTGGTGAAGT	CCTGTTACCA	GGACAATGGT
	301	

TGCCAAGGAC

GCCAGCAACG CGCCTTTTT ACGGTTCCTG

GCCGGAAAAA

CGGTCGTTGC

TACCTTTTTG

CCGCCTCGGA

GGCGGAGCCT ATGGAAAAAC

651

AGCGTCGATT TTTGTGATGC TCGTCAGGGG

CTCTGACTTG GAGACTGAAC

GTTTCGCCAC CAAAGCGGTG

601

TCGCAGCTAA AAACACTACG

AGCAGTCCCC

Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

		ACCTGAGTTC	TGCTATCAAT	GGCCTATTCC	ACCTGAGTTC TGCTATCAAT GGCCTATTCC GCGTCGCCAG CCCGACTTGC	CCCGACTTGC	
	401	GGGGGTTCGT CCCCCAAGCA	GGGGGTTCGT GCACACAGCC CAGCTTGGAG CGAACGACCT CCCCCAAGCA CGTGTGTCGG GTCGAACCTC GCTTGCTGGA	CAGCTTGGAG GTCGAACCTC	CGAACGACCT GCTTGCTGGA	ACACCGAACT TGTGGCTTGA	
	451	GAGATACCTA CTCTATGGAT	CAGCGTGAGC GTCGCACTCG	TATGAGAAAG ATACTCTTTC	TATGAGAAAG CGCCACGCTT ATACTCTTTC GCGGTGCGAA	CCCGAAGGGA GGGCTTCCCT	
O IF OTT	501	GAAAGGCGGA CTTTCCGCCT	CAGGTATCCG GTCCATAGGC	GTAAGCGGCA CATTCGCCGT	CAGGTATCCG GTAAGCGGCA GGGTCGGAAC AGGAGAGCGC GTCCATAGGC CATTCGCCGT CCCAGCCTTG TCCTCTCGCG BSSSI	AGGAGAGCGC TCCTCTCGCG BSSSI	
TO CHEUT /SHI E 9	551	ACGAGGGAGC TGCTCCCTCG BssSI	TTCCAGGGG	TTCCAGGGG AAACGCCTGG AAGGTCCCCC TTTGCGGACC	TATCTTTATA ATAGAAATAT	GTCCTGTCGG CAGGACAGCC	

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Figure 33: functional map and sequence of pCAL module M14-Ext2 (continued)

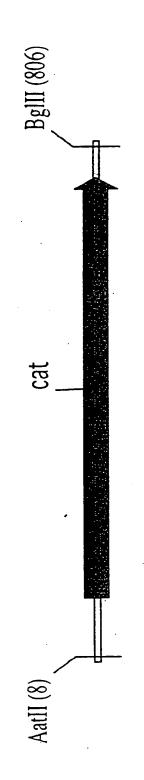
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GCCTTTTGCT GGCCTTTTGC TCACATGGCT AGC CGGAAAACGA CCGGAAAACG AGTGTACCGA TCG

701

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Figure 34: functional map and sequence of pCAL module M17



M17 813 bp

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Figure 34: functional map and sequence of pCAL module M17 (continued)

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⊣	GGGACGTCGG	GTGAGGTTCC	CGG GTGAGGTTCC AACTTTCACC ATAATGAAAT AAGATCACTA	ATAATGAAAT A	AAGATCACTA
	CCCTGCAGCC	GCC CACTCCAAGG	TTGAAAGTGG	TATTACTTTA	GCC CACTCCAAGG TTGAAAGTGG TATTACTTTA TTCTAGTGAT

CCGGGCGTAT TTTTTGAGTT ATCGAGATTT TCAGGAGCTA AGGAAGCTAA	AGTCCTCGAT TCCTTCGATT
TCAGGAGCTA	AGTCCTCGAT
ATCGAGATTT	ACTCAA TAGCTCTAAA
TTTTGAGTT	AAAAACTCAA
CCGGGCGTAT	GGCCCGCATA
51	

<b></b>	101	AATGGAGAAA AAAATCACTG GATATACCAC TTACCTCTTT TTTTAGTGAC CTATATGGTG	AAAATCACTG TTTTAGTGAC	GATATACCAC CTATATGGTG	CGTTGATATA TCCCAATGGC GCAACTATAT AGGGTTACCG	TCCCAATGGC AGGGTTACCG
<b></b>	151	ATCGTAAAGA TAGCATTTCT	ATCGTAAAGA ACATTTTGAG GCATTTCAGT CAGTTGCTCA ATGTACCTAT TAGCATTTCT TGTAAAACTC CGTAAAGTCA GTCAACGAGT TACATGGATA	GCATTTCAGT CGTAAAGTCA	CAGTTGCTCA ATGTACCTAT GTCAACGAGT TACATGGATA	ATGTACCTAT TACATGGATA

ACCG TTCAGCTGGA TATTACGGCC TTTTTAAAGA CCGTAAAGAA	TIGGC AAGTCGACCT ATAATGCCGG AAAAATTTCT GGCATTTCTT
TTTTAAAGA	AAAAATTTCT
TATTACGGCC	ATAATGCCGG
TTCAGCTGGA	AAGTCGACCT
AACCAGACCG	TTGGTCTGGC
201	

PCTT GCCCGCCTGA	AGAA CGGGCGGACT
AAGTTTTATC CGGCCTTTAT TCACATTCTT GCCCGCCTGA	AGTGTAAGAA
CGGCCTTTAT	AATAG GCCGGAAATA
AAGTTTTATC	GTG TTCAAAATAG
AAATAAGCAC	TTTATTCGTG
251	

TGAGCTGGTG	ACTCGACCAC	AGCAAACTGA
CTCA CCCGGAGTIC CGTATGGCAA TGAAAGACGG TGAGCTGGTG	CTTACGAGT GGGCCTCAAG GCATACCGTT ACTTTCTGCC ACTCGACCAC	ATATGGGATA GTGTTCACCC TTGTTACACC GTTTTCCATG AGCAAACTGA
CGTATGGCAA	GCATACCGTT	TTGTTACACC
CCCGGAGTTC	GGGCCTCAAG	GTGTTCACCC
TGAATGCTCA	ACTTACGAGT	ATATGGGATA
301		351

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nal map and sequence of pCAL module M17 (continued)
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		TATACCCTAT	CACAAGTGGG	AACAATGTGG	CAAAAGGTAC	TCGTTTGACT
	401	AACGTTTTCA TTGCAAAAGT	TCGCTCTGGA AGCGAGACCT	GTGAATACCA CACTTATGGT	CGACGATTTC GCTGCTAAAG	CGGCAGTTTC GCCGTCAAAG
	451	TACACATATA	TTCGCAAGAT AAGCGTTCTA	GTGGCGTGTT CACCGCACAA	ACGGTGAAAA TGCCACTTTT	CCTGGCCTAT GGACCGGATA
CUDO	501	TTCCCTAAAG AAGGGATTTC	GGTTTATTGA CCAAATAACT	GAATATGTTT CTTATACAAA	TTCGTCTCAG AAGCAGAGTC	CCAATCCCTG GGTTAGGGAC
TITLITE OLE	551	GGTGAGTTTC CCACTCAAAG	ACCAGTTTTG TGGTCAAAAC	ATTTAAACGT TAAATTTGCA	AGCCAATATG TCGGTTATAC	GACAACTTCT CTGTTGAAGA
	601	TCGCCCCCGT	TTTCACTATG AAAGTGATAC	GGCAAATATT CCGTTTATAA	ATACGCAAGG	CGACAAGGTG GCTGTTCCAC
	651	CTGATGCCGC GACTACGGCG	TGGCGATTCA ACCGCTAAGT	GGTTCATCAT CCAAGTAGTA	GCCGTTTGTG CGGCAAACAC	ATGGCTTCCA
	701	TGTCGGCAGA ACAGCCGTCT	ATGCTTAATG TACGAATTAC	AATTACAACA TTAATGTTGT	GTACTGCGAT CATGACGCTA	GAGTGGCAGG CTCACCGTCC
	751	GCGGGGCGTA	ATTTTTAA	ATTTTTTAA GGCAGTTATT	GGGTGCCCTT	AAACGCCTGG

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Figure 34; functional map and sequence of pCAL module M17 (continued)

CGCCCCGCAT TAAAAAATT CCGTCAATAA CCCACGGGAA TTTGCGGACC

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TCC TGCTAGATCT

ACGATCTAGA 801

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Figure 35: functional map and sequence of modular vector pCAL4

functional ssori Bsr61 (612) Fsel (599) Hind111 (515) gill supershort Pac! (579) GenII-Nick Xmn1 (310) Ban [1 (919) Nhei (1076) replication start EcoRI (1) 2755 bp pCAL4 Sph1 (2749) BSSSI (1254) Colel Ext2 origin **Kbal** (2739) Hatil (2608) lac p/o BgIII (1803) cat

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Figure 35: functional map and sequence of modular vector pCAL4 (continued)

	EcoRI				
	~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~				
$\vdash$	AATTCGAGCA	GAGCA GAAGCTGATC TCTGAGGAGG ATCTGTAGGG TGGTGGCTCT	TCTGAGGAGG	ATCTGTAGGG	TGGTGGCTCT
	TTAAGCTCGT	CTCGT CTTCGACTAG AGACTCCTCC TAGACATCCC ACCACCGAGA	AGACTCCTCC	TAGACATCCC	ACCACCGAGA

STG ATTTTGATTA TGAAAGATG GCAAACGCTA ATAAGGGGGC	ACTAAT ACTTTTCTAC CGTTTGCGAT TATTCCCCCG
TG GCAAACGCTA ATAA	CGTTTGCGAT TAT
TGAAAAGATG	ACTITITIAC
ATTTTGATTA	TAAAACTAAT
GGTTCCGGTG	CCAAGGCCAC
51	

CGAA AATGCCGATG AAAACGCGCT ACAGTCTGAC GCTAAAGGCA	CGATTTCCGT	TGGTTTCATT
ACAGTCTGAC	TGTCAGACTG	CTGCTATCGA
AAAACGCGCT	TTTTGCGCGA	GATTACGGTG
AATGCCCATG	GGCTT TTACGGCTAC TTTTGCGCGA TGTCAGACTG CGATTTCCGT	ATTC TGTCGCTACT GATTACGGTG CTGCTATCGA TGGTTTCATT
TATGACCGAA	ATACTGGCTT	AACTTGATTC
101		151
	SUE	STITUT

ACCAAAGTAA	GTGATTTTGC	CACTAAAACG
AAG ACAGCGATGA CTAATGCCAC GACGATAGCT ACCAAAGTAA	STIT CCGGCCTIGC TAATGGTAAT GGTGCTACTG GTGATTTTGC	LAAA GGCCGGAACG ATTACCATTA CCACGATGAC CACTAAAACG
CTAATGCCAC	TAATGGTAAT	ATTACCATTA
ACAGCGATGA	CCGGCCTTGC	GGCCGGAACG
TTGAACTAAG	GGTGACGTTT	CCACTGCAAA
	201	
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ATCGGTTGAA TATTTACCTT CCCTCCCTCA GGGAGGGAGT ATAAATGGAA TAATGAATAA TTTCCGTCAA ATTACTTATT AAAGGCAGTT 301

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Figure 35: functional map and sequence of modular vector pCAL4 (continued)

	GTTAAAATTC CAATTTTAAG	TTAATATTTT AATTATAAAA	ATTGTAAACG TAACATTTGC	TGTACATGAA ACATGTACTT	TGGGGGGGGG	601
				BsrGI		
	9922992222	AAGGGGGGG	CGTTTAATTA GCAAATTAAT	TTTTGTCTGC AAAACAGACG	GCGACATTTT	551
	FSEI		Paci			
	CGCAGATTGT GCGTCTAACA	TGAAAAATGG ACTTTTTACC	ACCTGTGAAG TGGACACTTC	HindIII ~~~~~ GATAAGCTTG CTATTCGAAC	AAGGAGTCTT TTCCTCAGAA	501
	ACTGCGTAAT TGACGCATTA	TTGCTAACAT AACGATTGTA	TTTTCTACGT AAAAGATGCA	TATGTATGTA ATACATACAT	TTGCCACCTT AACGGTGGAA	451
	CTTTTATATG GAAAATATAC	CTTTGCGTTT GAAACGCAAA	TCCGTGGTGT	ATAAACTTAT TATTTGAATA	TTGTGACAAA AACACTGTTT	401
•	TTTCTATTGA AAAGATAACT	CCATATGAAT GGTATACTTA	CGCTGGTAAA GCGACCATTT	TTGTCTTTGG AACAGAAACC	TGTCGCCCTT	351

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

	651	GCGTTAAATT CGCAATTTAA	TTTGTT&AAT AAACAATTTA	CAGCTCATTT GTCGAGTAAA	TTTAACCAAT AAATTGGTTA	AGGCCGAAAT TCCGGCTTTA	
	701	CGGCAAAATC	CCTTATAAAT GGAATATTTA	CAAAAGAATA GTTTTCTTAT	GACCGAGATA CTGGCTCTAT	GGGTTGAGTG CCCAACTCAC	•
	751	TTGTTCCAGT AACAAGGTCA	TTGGAACAAG	AGTCCACTAT TCAGGTGATA	TAAAGAACGT ATTTCTTGCA	GGACTCCAAC CCTGAGGTTG	
	801	GTCAAAGGGC	GAAAAACCGT CTTTTTGGCA	CTATCAGGGC GATÁGTCCCG	GATGGCCCAC CTACCGGGTG	TACGAGAACC ATGCTCTTGG	
	851	ATCACCCTAA TAGTGGGATT	TCAAGTTTTT AGTTCAAAAA	TGGGGTCGAG	GTGCCGTAAA CACGGCATTT	GCACTAAATC CGTGATTTAG	
· = 00\			BanII				
	901	GGAACCCTAA CCTTGGGATT	AGGGAGCCCC TCCCTCGGGG	CGATTTAGAG GCTAAATCTC	CTTGACGGGG	AAAGCCGGCG TTTCGGCCGC	
	951	AACGTGGCGA TTGCACCGCT	GAAAGGAAGG CTTTCCTTCC	GAAGAAAGCG CTTCTTTCGC	AAAGGAGCGG	GCGCTAGGGC CGCGATCCCG	

		•				
ອວອວອອວອອ	AAAGGCCAGC TTTCCGGTCG	TTTCCATAGG AAAGGTATCC	GTCAGAGGTG CAGTCTCCAC	CCTGGAAGCT GGACCTTCGA	ATACCTGTCC TATGGACAGG	CACGCTGTAG GTGCGACATC
AACCACCACA TTGGTGGTGT	CATGTGAGCA GTACACTCGT	TGCTGGCGTT ACGACCGCAA	CGACGCTCAA GCTGCGAGTT	GGCGTTTCCC CCGCAAAGGG	CGCTTACCGG GCGAATGGCC	TCTCATAGCT AGAGTATCGA
4 (continued) CGCTGCGCGT GCGACGCGCA	NheI ~~~~~ GCGTGCTAGC CGCACGATCG	AAGGCCGCGT TTCCGGCGCA	TCACAAAAAT AGTGTTTTTA	AAAGATACCA TTTCTATGGT	CCGACCCTGC	CGTGGCGCTT GCACCGCGAA
e of modular vector pCAL GTAGCGGTCA CATCGCCAGT	GCTACAGGGC CGATGTCCCG	GAACCGTAAA CTTGGCATTT	CTGACGAGCA	ACAGGACTAT TGTCCTGATA	CTCTCCTGTT GAGAGGACAA	CTTCGGGAAG GAAGCCCTTC
Figure 35: functional map and sequence of modular vector pCAL4 (continued) 1001 GCTGGCAAGT GTAGCGGTCA CGCTGC CGTCGCCAGT GCGACC	TTAATGCGCC AATTACGCGG	AAAAGGCCAG TTTTCCGGTC	CTCCGCCCCC	GCGAAACCCG CGCTTTGGGC	BssSI ~~~~~ CCCTCGTGCG GGGAGCACGC	GCCTTTCTCC CGGAAAGAGG
Figure 35: fu 1001	1051	1101	1151	1201	1251	1301

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

	1351	GTATCTCAGT CATAGAGTCA	TCGGTGTAGG AGCCACATCC	TCGTTCGCTC AGCAAGCGAG	CAAGCTGGGC GTTCGACCCG	TGTGTGCACG ACACACGTGC
	1401	AACCCCCCGT TTGGGGGGCA	TCAGCCCGAC AGTCGGGCTG	CGCTGCGCCT GCGACGCGGA	TATCCGGTAA ATAGGCCATT	
8	1451	GAGTCCAACC	CGGTAAGACA GCCATTCTGT	CGACTTATCG GCTGAATAGC	CCACTGGCAG GGTGACCGTC	
UBSTITUTE	1501	TAACAGGATT ATTGTCCTAA	AGCAGAGCGA TCGTCTCGCT	GGTATGTAGG CCATACATCC	CGGTGCTACA GCCACGATGT	
SHEET (RUI	1551	AGTGGTGGCC TCACCACCGG	TAACTACGGC ATTGATGCCG	TACACTAGAA ATGTGATCTT	GAACAGTATT CTTGTCATAA	
_E 26)	1601	GCTCTGCTGT CGAGACGACA	AGCCAGTTAC TCGGTCAATG	CTTCGGAAAA GAAGCCTTTT.	AGAGTTGGTA TCTCAACCAT	
	1651	CGGCAAACAA GCCGTTTGTT	ACCACCGCTG TGGTGGCGAC	GTAGCGGTGG	TTTTTTTGTT AAAAAAACAA	
	1701	AGATTACGCG	CAGAAAAAAA GTCTTTTTTT	GGATCTCAAG CCTAGAGTTC	AAGATCCTTT TTCTAGGAAA	

Figure 35: functional map and sequence of modular vector pCAL4 (continued)

GGATTTTGGT CCTAAAACCA	ттааааааат аатттттта	CATTAAGCAT GTAATTCGTA	TGAATCGCCA ACTTAGCGGT	CATAGTGAAA GTATCACTTT	CAAAACTGGT GTTTTGACCA	TCAATAAACC AGTTATTTGG
TCACGTTAAG AGTGCAATTC	AATAACTGCC	TGTTGTAATT	ATGATGAACC TACTACTTGG	AATATTTGCC TTATAAACGG	ACGTTTAAAT TGCAAATTTA	AAACATATTC TTTGTATAAG
GAACGAAAAC CTTGCTTTTG	TAAGGGCACC ATTCCCGTGG	ATCGCAGTAC TAGCGTCATG	CACAAACGGC GTGTTTGCCG	CCTTGCGTAT GGAACGCATA	CATATTGGCT GTATAACCGA	CTGAGACGAA GACTCTGCTT
ACGCTCAGTG TGCGAGTCAC	ACCAGGCGTT TGGTCCGCAA	CCTGCCACTC	TGGAAGCCAT ACCTTCGGTA	CACCTTGTCG GTGGAACAGC	AGAAGTTGTC TCTTCAACAG	CAGGGATTGG GTCCCTAACC
ACGGGGTCTG	BglII ~~~~~~ CAGATCTAGC GTCTAGATCG	TACGCCCCGC	TCTGCCGACA AGACGGCTGT	GCGGCATCAG CGCCGTAGTC	ACGGGGGGGA TGCCCCCGCT	GAAACTCACC CTTTGAGTGG
1751	1801	1851	1901	1951	2001	2051
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GAGTTTTACA

TGACTTTACG

ACTCGTTGAC

TATCCATGTA

GCCAGACCAA

GTCACTAAAA CAGTGATTTT

GTGGTATATC CACCATATAG

TATATCAACG ATATAGTTGC

GCCATTGGGA CGGTAACCCT

AGAAATGCTA

TCTTTACGAT

2451

ATCTTGCGAA TAGAACGCTT	TCCAGAGCGA AGGTCTCGCT	GGGTGAACAC	GAACTCCGGG CTTGAGGCCC	GATAAAACTT CTATTTTGAA	TCCAGCTGAA AGGTCGACTT	CTCAAAATGT
AACACGCCAC TTGTGCGGTG	TGGTATTCAC ACCATAAGTG	GGTGTAACAA CCACATTGTT	TTGCCATACG AACGGTATGC	ATAAAGGCCG TATTTCCGGC	GGCCGTAATA	ACTGAAATGC
f (continued) TTTTCACCGT AAAAGTGGCA	GAAATCGTCG CTTTAGCAGC	CATGGAAAAC GTACCTTTTG	CCGTCTTTCA GGCAGAAAGT	AAGAATGTGA TTCTTACACT	TCTTTAAAAA AGAAATTTTT	TGAGCAACTG
e of modular vector pCAL <sup>4</sup> ATAGGCCAGG TATCCGGTCC	GAAACTGCCG CTTTGACGGC	TCAGTTTGCT AGTCAAACGA	CACCAGCTCA GTGGTCGAGT	TCAGGCGGGC AGTCCGCCCG	TTCTTTACGG AAGAAATGCC	ATAGGTACAT
Figure 35: functional map and sequence of modular vector pCAL4 (continued) 2101 CTTTAGGGAA ATAGGCCAGG TTTTCAGGCAACTCCGGTCC AAAAGT	TATATGTGTA ATATACACAT	TGAAAACGTT ACTTTTGCAA	TATCCCATAT ATAGGGTATA	TGAGCATTCA ACTCGTAAGT	GTGCTTATTT CACGAATAAA	CGGTCTGGTT
Figure 35: fui 2101	2151	2201	2251	2301	2351	2401

Figure 35: functional map and sequence of modular vector  $pCAL^{\frac{1}{2}}$  (continued)

WO 97/08	3320	•			PC	CT/EP96/03
AACTCAAAAA TTGAGTTTTT	GGAACCTCAC CCTTGGAGTG	AGGCTTTACA TCCGAAATGT	GGATAACAAT CCTATTGTTA	xbal sphi ~~~~~~~~~~ rcr agagcargcg aga rcrcgracgc		
AAATCTCGAT TTTAGAGCTA	GGTGAAAGTT CCACTTTCAA	TAGGCACCCC	AATTGTGAGC TTAACACTCG	XbaI ~~~~ ACGAATTTCT A TGCTTAAAGA T		
TAGCTCCTGA ATCGAGGACT	ATTTCATTAT TAAAGTAATA	GCTCACTCAT	TGTTGTGG ACAACACACC	GACCATGATT CTGGTACTAA	-	
TTAGCTTCCT AATCGAAGGA	TAGTGATCTT ATCACTAGAA	ATGTGAGTTA TACACTCAAT	CCGGCTCGTA GGCCGAGCAT	AAACAGCTAT TTTGTCGATA		
TTTCTCCATT AAAGAGGTAA	ATACGCCCGG TATGCGGGCC	Aatll ~~~~~~ CCGACGTCTA GGCTGCAGAT	CTTTATGCTT GAAATACGAA	TTCACACAGG	EcoRI	ეეეეე ეეეეე
2501	2551	2601	2651	2701		2751

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**M2** 173 bp

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211111

GGCTTTACAC CCGAAATGTG AGGCACCCCA TCCGTGGGGT GAGTGAGTAA CTCACTCATT TGTGAGTTAG ACACTCAATC CTGCAGAATT GACGICTTAA

CTATTGTTAA GATAACAATT ATTGTGAGCG TAACACTCGC GTTGTGTGGA CAACACACCT GCCGAGCATA CGGCTCGTAT TTTATGCTTC AAATACGAAG 51

XmnI

XbaI

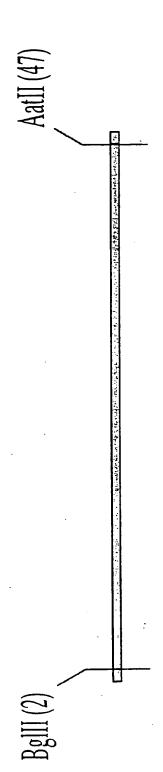
GTATAATGTA CATATTACAT GAATAACTTC CTTATTGAAG ACCATGTCTA TTGTCGATAC TGGTACAGAT AACAGCTATG TCACACAGGA AGTGTGTCCT

SphI

ACG AGTTATCGCA TGC TCAATAGCGT CGCTATACGA GCGATATGCT 151

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101



**M3** 47 bp

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

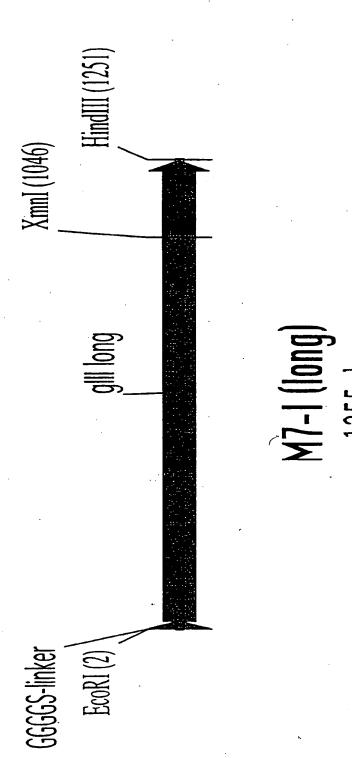
™ 3:

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TGACGIC ACTGCAG ATGCTTCAAT ATGTATGCTA TACGAAGTTA TACATACGAT ATGCTTCAAT ACTTCGTATA TGAAGCATAT AGATCTCATA TCTAGAGTAT

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TCTGAGGGTG TGGAGGACTC CTCTCGACGG GAGAGCTGCC TTTCAACAAA AAAGACGACA GAATGCTACA CATGTACCCA AGACTCCCAC ACCTCCTGAG TTTCTGCTGT CTTACGATGT GTACATGGGT AAAGTTGTTT CCCACCACCG GCGGTACTAA TATATCAACC ATATAGTTGG GTCACAATGC CGCCATGATT GGGTGGTGGC TAACGTCTGG ATTGCAGACC GCTGTCTGTG CGACAGACAC CAGTGTTACG GAAACGGTTG CTTTGCCAAC TAAGTAAATG TTGATACTCC ACTGCTTTGA CTGAAAATGA GACTTTTACT TCTGAGGGTG AGACTCCCAC GGGCTATACT CCCGATATGA ACGCACGCGA TGACGAAACT AACTATGAGG TGCGTGCGCT ATTCATTAC CCCACCGCCA AGCAATGCGA AAACATGACC GAACGATAGG CACCTATTCC GTGGATAAGG TTTGTACTGG CTTGCTATCC GGGTGGCGGT CACCACCTAG TCGTTACGCT GTGGTGGATC CATACAGAAA GTATGTCTTT TACGGTGATA CTTAAGCCAC TCGTTTTAGG TTTGAAATCT CCGCAACATC TCCTATTGGG AGGATAACCC GCGGTTCTGA CGCCAAGACT ATGCCACTAT GAATTCGGTG AGCAAAATCC AAACTTTAGA GGCGTTGTAG 51 151 201 251 301 101

Figure 35a. Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

TTCTGAGGGT AAGACTCCCA	AGGGTGGCGG TCCCACCGCC	GGTGGCTCTG CCACCGAGAC	CTCTGAGGGT GAGACTCCCA	CTGGTGGCGG GACCACCGCC	701
GGTGGTGGTT CCACCACCAA	CGGCGGCTCT GCCGCCGAGA	TCAATGCTGG AGTTACGACC	CAACCTCCTG	TGACCTGCCT	651
GCCAATCGTC CGGTTAGCAG	GAATATCAAG	ATTTGTTTGT TAAACAAACA	ATGAGGATTT TACTCCTAAA	TCTGGCTTTA AGACCGAAAT	601
CGCTTTCCAT GCGAAAGGTA	TCAGAGACTG AGTCTCTGAC	AACGGTAAAT TTGCCATTTA	CGCTTACTGG GCGAATGACC	CCATGTATGA GGTACATACT	551
TCATCAAAAG AGTAGTTTTC	CACTCCTGTA GTGAGGACAT	ATTACCAGTA TAATGGTCAT	GTTAAAACTT CAATTTTGAA	CACTGACCCC	501
TTACTCAAGG AATGAGTTCC	ACGGGCACTG TGCCCGTGAC	AACTGTTTAT TTGACAAATA	AGGGGGCATT TCCCCCGTAA	CGAAATAGGC GCTTTATCCG	451
TAATAGGTTC ATTATCCAAG	TGTTTCAGAA ACAAAGTCTT	AATACTTTCA TTATGAAAGT	TCAGCCTCTT AGTCGGAGAA	TTGAGGAGTC AACTCCTCAG	401
AATCCTTCTC TTAGGAAGAG	CGCTAATCCT GCGATTAGGA	AGCAAAACCC TCGTTTTGGG	CCTGGTACTG GGACCATGAC	CACTTATCCG GTGAATAGGC	351

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

GCCCTTTTGT CGGGAAAACA	GTTGAATGTC CAACTTACAG	CCCTCAATCG GGGAGTTAGC	TACCTTCCAT ATGGAAGGTA	CGTCAATATT GCAGTTATAA	1051	
GAATAATTTC CTTATTAAAG	CACCTTTAAT GTGGAAATTA	GGTGATAATT CCACTATTAA	AGTCGGTGAA TCAGCCACTT	AAATGGCTCA TTTACCGAGT	1001	
XmnI		,				ויו ד ממ
TCTAATTCCC AGATTAAGGG	TTTTGCTGGC AAAACGACCG	CTACTGGTGA GATGACCACT	GGTAATGGTG CCATTACCAC	CCTTGCTAAT GGAACGATTA	951	E CHEET (DI
ACGTTTCCGG TGCAAAGGCC	TTCATTGGTG AAGTAACCAC	TATCGATGGT ATAGCTACCA	ACGGTGCTGC TGCCACGACG	GCTACTGATT CGATGACTAA	901	CHECTIT
TGATTCTGTC ACTAAGACAG	AAGGCAAACT TTCCGTTTGA	TCTGACGCTA AGACTGCGAT	CGCGCTACAG GCGCGATGTC	CCGATGAAAA GGCTACTTTT	851	
ACCGAAAATG TGGCTTTTAC	GGGGCCTATG CCCCCGATAC	ACGCTAATAA TGCGATTATT	AAGATGGCAA TTCTACCGTT	TGATTATGAA ACTAATACTT	801	
CCGGTGATTT GGCCACTAAA	GGCTCTGGTT CCGAGACCAA	TTCCGGTGGT AAGGCCACCA	AGGGAGGCGG TCCCTCCGCC	GGGGGCTCTG	751	

(continued)
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maps and sequences of
Figure 35a: Functional

ATTGT GACAAAATAA	ACA CTGTTTTATT
TATTGAT	G ATAACTAACA
ATGAATTTTC TATTGATTGT	TACTTAAAAG
GGTAAACCCT	CCATTTGGGA
CTTTGGCGCT	GAAACCGCGA
1101	

CACCTTTATG GTGGAAATAC ATATACAACG TATATGTTGC GCGTTTCTTT CGCAAAGAAA ACCACAGAAA TGGTGTCTTT ACTTATTCCG TGAATAAGGC 1151

HindIII

AGTCTTGATA TCAGAACTAT CGTAATAAGG GCATTATTCC ATTGTATGAC TAACATACTG CTACGTTTGC GATGCAAACG TATGTATTTT 1201

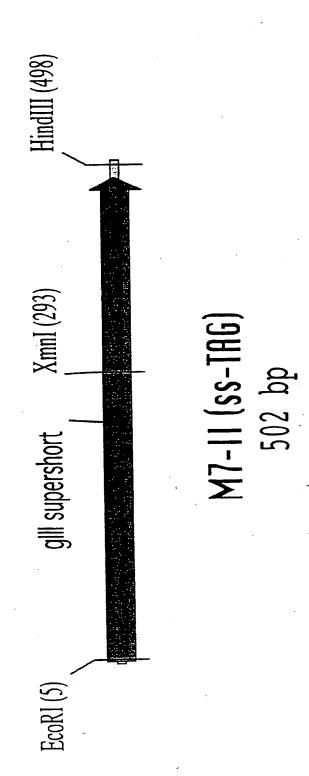
ATACATAAAA

HindI AGCTT 1111 1251

TCGAA

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### M 7-II (SS-TAG)

ECORI

GTGATTTTGA CACTAAAACT TCTGGTTCCG AGACCAAGGC GCCACCACCG CGGTGGTGGC CTCCGCCAAG GAGGCGGTTC GCCCTTAAGC CGGGAATTCG

GAAAATGCCG CTTTTACGGC CCGATACTGG GGCTATGACC CTAATAAGGG GATTATTCCC TACCGTTTGC ATGGCAAACG AATACTTTTC TTATGAAAAG 51

101

TICIGICECT CGTTTGAACT AAGACAGCGA GCAAACTTGA CGATGTCAGA CTGCGATTTC GACGCTAAAG GCTACAGTCT TACTTTGCG ATGAAAACGC

TITCCGGCCT AAAGGCCGGA TAACCACTGC ATTGGTGACG GCTACCAAAG CGATGGTTTC CACGACGATA GTGCTGCTAT TGACTAATGC ACTGATTACG 151

AATTCCCAAA TTAAGGGTTT GACCACTAAA ACGACCGAGA TGCTGGCTCT CTGGTGATTT AATGGTGCTA TTACCACGAT ACGATTACCA TGCTAATGGT 201

XmnI

TAATTTCCGT ATTAAAGGCA CTTTAATGAA GAAATTACTT GATAATTCAC CTATTAAGTG CGGTGACGGT GCCACTGCCA TGGCTCAAGT ACCGAGTTCA 251

	CTTTTGT
ıtinued)	GAATGTCGCC
and sequences of additional pCAL vector modules and pCAL vectors (continued)	TELLILIO DOSCIEDA VE CENTRAL CARRESTO CENTRALICADO
bbs in sandings has seen leading in the	Figure 35a: Functional maps and sequences of

CTT GAAAACAGAA CTTACAGCGG AGTTAGCCAA T CHAICGGI I GAAGGGAGGG CHICCCICC CAATATTAC GTTATAAATG 301

TTTTATTTGA AAAATAAACT TGATTGTGAC ACTAACACTG TTAAAAGATA AATTTTCTAT AAACCATATG TTTGGTATAC TGGCGCTGGT ACCGCGACCA 351

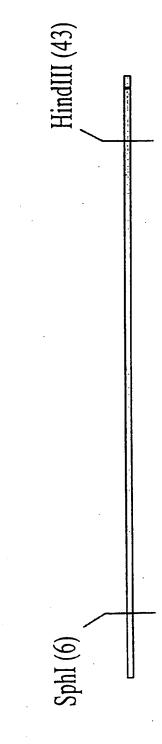
CTTTATGTAT ATGTTGCCAC TTTCTTTAT TGTCTTTGCG ATAAGGCACC TATTCCGTGG 401

GAAATACATA TACAACGGTG AAAGAAAATA ACAGAAACGC

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GAACTATTCG CTTGATAAGC TTATTCCTCA AATAAGGAGT GTATGACGCA CATACTGCGT GCAAACGATT CGTTTGCTAA CATAAAAGAT GTATTTTCTA 451

TT501



**X8** 47 bp

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

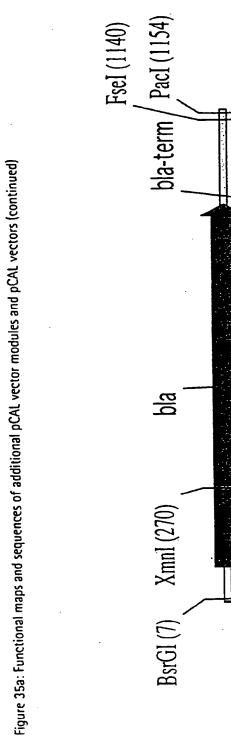
SphI

TACGAAGTTA ATGTACGCTA ACTTCGTATA GCATGCCATA

TAAGCTT

ATTCGAA

ATGCTTCAAT TACATGCGAT TGAAGCATAT CGTACGGTAT



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BsrGI

ATGAGACAAT AACCCTGATA	TATGAGTATT CAACATTTCC
TACTCTGTTA TTGGGACTAT	ATACTCATAA GTTGTAAAGG
GTATCCGCTC	AAAGGAAGAG
CATAGGCGAG	TTTCCTTCTC
AC ATTCAAATAT	CAA TAATATTGAA AAAGGAAGAG
ATG TAAGTTTATA	GTT ATTATAACTT TTTCCTTCTC
GGGGGTGTAC	AATGCTTCAA
CCCCCACATG	TTACGAAGTT
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GITGIAAAGG	TGTTTTGCT	GGA ATAAGGGAAA AAACGCCGTA AAACGGAAGG ACAAAAACGA
sil Alialaacil lilecileie Alaciealaa gilgiaaagg	CCT TATTCCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT	AAACGGAAGG
דוררוורור	TTTGCGGCAT	AAACGCCGTA
ALLALAACLL	TATTCCCTTT	ATAAGGGAAA
LIACGAAGII	GTGTCGCCCT	CACAGCGGGA
	101	
SU	BSTI	TUT

ACAAAAACGA	AGTTGGGTGC TCAACCCACG	ATCCTTGAGA TAGGAACTCT		
CACAGCGGA ATAAGGGAAA AAACGCCGTA AAACGGAAGG ACAAAAACGA	AAA CGCTGGTGAA AGTAAAAGAT GCTGAGGATC AGTTGGGTGC TTT GCGACCACTT TCATTTTCTA CGACTCCTAG TCAACCCACG	GCTCACCCA ATGTAGCTTG ACCTAGAGTT GTCGCCATTC TAGGAACTCT		
AAACGCCGTA	AGTAAAAGAT TCATTTTCTA	TGGATCTCAA ACCTAGAGTT		
ATAAGGGAAA	ACCCAGAAA CGCTGGTGAA TGGGTCTTT GCGACCACTT	TACATCGAAC ATGTAGCTTG		
CACAGCGGGA	CACCCAGAAA GTGGGTCTTT	GCGAGTGGGT		
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		TGAGCACTTT TAAAGTTCT
XmnI		TCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT TAAAGTTCT
÷	-	GTTTTCGCCC
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CAAAAAGCGGG GCTTCTTGCA AAAGGTTACT ACTCGTGAAA ATTTCAAGAC

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Figure 35a: Functional ma	

AGCAACTCGG	TCACCAGTCA	ATGCAGTGCT
TCGTTGAGCC	AGTGGTCAGT	TACGTCACGA
GCCGGGCAAG AGCAACTCGG	GGTTGAGTAC	TAAGAGAATT
CGGCCCGTTC TCGTTGAGCC	CCAACTCATG	ATTCTCTTAA
CCGTATTGAC	AGAATGACTT	GGCATGACAG
GGCATAACTG	TCTTACTGAA	CCGTACTGTC
CGGTATTATC	CACTATTCTC	TCTTACGGAT
GCCATAATAG	GTGATAAGAG	AGAATGCCTA
CTATGTGGCG	TCGCCGCATA	CAGAAAAGCA
GATACACCGC	AGCGGCGTAT	GTCTTTTCGT
301	351	401

ACCA TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT	ACTGTTGCTA
AACTTACTTC	TTGAATGAAG ACTGTTGCTA
CACTGCGGCC	GTGACGCCGG
TGAGTGATAA	GGT ACTCACTATT
GCCATAACCA	CGGTATTGGT
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	ACCG AAGGAGCTAA CCGCTTTTTT GCACAACATG GGGGATCATG	CCCCTAGTAC	
	GCACAACATG	rggc rrccrcgarr ggcgaaaaaa cgrgrrgrac ccccragrac	
	CCGCTTTTTT	GGCGAAAAAA	
	AAGGAGCTAA	TICCICGAIT	
	CGGAGGACCG	CCCTCCTGGC	
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CATACCAAAC	GTATGGTTTG
GAACCGGAGC TGAATGAAGC CA	ACTTACTTCG
GAACCGGAGC	CC CTTGGCCTCG
rcgttgg	ACTAGCAACC
TAACTCGCCT TGA	ATTGAGCGGA
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	701	ACTGGATGGA TGACCTACCT	GGCGGATAAA CCGCCTATTT	GTTGCAGGAC	CACTTCTGCG GTGAAGACGC	CTCGGCCCTT GAGCCGGGAA	
	751	CCGGCTGGCT	GGTTTATTGC CCAAATAACG	TGATAAATCT ACTATTTAGA	GGAGCCGGTG CCTCGGCCAC	AGCGTGGGTC TCGCACCCAG	
	801	TCGCGGTATC AGCGCCATAG	ATTGCAGCAC TAACGTCGTG	TGGGGCCAGA	TGGTAAGCCC	TCCCGTATCG	
SUBS	851	TAGTTATCTA ATCAATAGAT	CACGACGGGG GTGCTGCCCC	AGTCAGGCAA TCAGTCCGTT	CTATGGATGA GATACCTACT	ACGAAATAGA TGCTTTATCT	
TITUTE SHE	901	CAGATCGCTG GTCTAGCGAC	AGATAGGTGC TCTATCCACG	CTCACTGATT GAGTGACTAA	AAGCATTGGG TTCGTAACCC	TAACTGTCAG ATTGACAGTC	
ET (RULE 26	951	ACCAAGTTTA TGGTTCAAAT	CTCATATATA GAGTATATAT	CTTTAGATTG GAAATCTAAC	ATTTAAAACT TAAATTTTGA	TCATTTTAA AGTAAAAATT	
5)	1001	TTTAAAAGGA AAATTTTCCT	TCTAGGTGAA AGATCCACTT	GATCCTTTTT CTAGGAAAAA	GATAATCTCA CTATTAGAGT	TGACCAAAAT ACTGGTTTTA	
	1051	CCCTTAACGT	GAGTTTTCGT CTCAAAAGCA	TCCACTGAGC	GTCAGACCCC	GTAGAAAAGA CATCTTTTCT	

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	FseI
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)	

CCCCCCCTT	GGGGGGGGAA
AGGATC TTCTTGAGAT CCTTTTGAT AATGGCCGGC CCCCCCTT	CCTAG AAGAACTCTA GGAAAAACTA TTACCGGCCG GGGGGGGAA
CCTTTTTGAT	GGAAAAACTA
TTCTTGAGAT	AAGAACTCTA
TCAAAGGATC	AGTTTCCTAG
1101	) 

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1151 AATTAAGGGG GGG TTAATTCCCC CCC

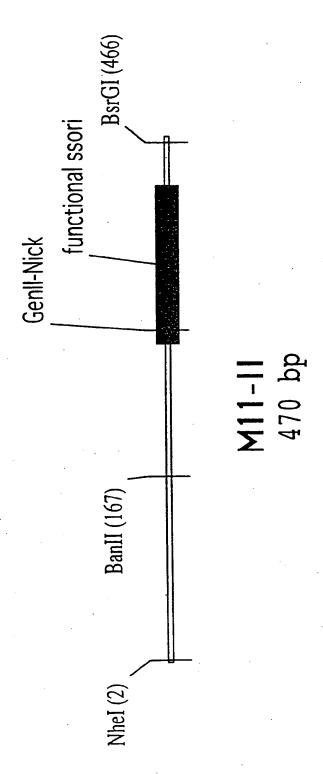


Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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₩.	GCTAGCACGC	GCCCTGTAGC CGGGACATCG	GGCGCATTAA CCGCGTAATT	ວວວອວວອວອວ	TGTGGTGGTT ACACCACCAA
51	ACGCGCAGCG	TGACCGCTAC	ACTTGCCAGC TGAACGGTCG	GCCCTAGCGC CGGGATCGCG	CCGCTCCTTT GGCGAGGAAA
101	CGCTTTCTTC GCGAAAGAAG	CCTTCCTTTC GGAAGGAAAG	TCGCCACGTT AGCGGTGCAA	CGCCGGCTTT GCGGCCGAAA	CCCCGTCAAG GGGGCAGTTC
151	CTCTAAATCG GAGATTTAGC	Banll CCCCGAGGGA	TTAGGGTTCC AATCCCAAGG	GATTTAGTGC CTAAATCACG	TTTACGGCAC
201	CTCGACCCCA GAGCTGGGGT	AAAAACTTGA TTTTTGAACT	TTAGGGTGAT AATCCCACTA	GGTTCTCGTA CCAAGAGCAT	GTGGGCCATC CACCCGGTAG
251	GCCCTGATAG	ACGGTTTTTC TGCCAAAAAG	GCCCTTTGAC	GTTGGAGTCC	ACGTTCTTTA TGCAAGAAAT

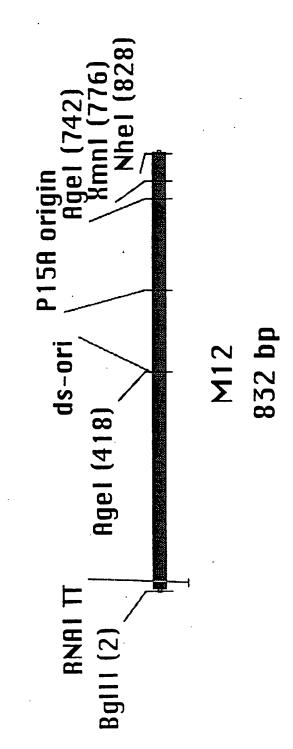
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	ACT CTTGTTCCAA ACTGGAACAA CACTCAACCC TATCTCGGTC	TGA GAACAAGGTT TGACCTTGTT GTGAGTTGGG ATAGAGCCAG
ontinued)	CACTCAACCC	GTGAGTTGGG
nces of additional pCAL vector modules and pCAL vectors (continued)	ACTGGAACAA	TGACCTTGTT
dditional pCAL vector mod	CTTGTTCCAA	GAACAAGGTT
I maps and sequences of ac	ATAGTGGACT	TATCACCTGA
Figure 35a: Functional maps and sequenc	301	

ATTGGTTAAA	TAACCAATTT
ATTTCGGCCT	TAAAGCCGGA
GATTTTGCCG	CTAAAACGGC
ATTTATAAGG	TAAATATTCC
TATTCTTTG	ATAAGAAAAC
351	

SCTG ATTTAACAAA AATTTAACGC GAATTTTAAC AAAATATTAA	CTTAAAATTG TTTTATAATT	
GAATTTTAAC	G CTTAAAATTG	
AATTTAACGC	TTAAATTGCG	
ATTTAACAAA	TAAATTGTTT	
AAATGAGCTG	TTTACTCGAC	
401		



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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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TTTTGGTCTG CGCGTAATCT GCGCATTAGA AAAACCAGAC GAACTCTAGC CTTGAGATCG AGATGATCTT TCTACTAGAA AGATCTAATA TCTAGATTAT

TTCGTAGGTT AAGCATCCAA TCCCGCCAAA AGGGCGGTTT ACCGCCTTGC TGGCGGAACG AAACGAAAAA TTTGCTTTTT CTTGCTCTGA GAACGAGACT 51

GAGGAGCGCA CTCCTCGCGT AACTGGCTTG TTGACCGAAC GAACCGAGGT CTTGGCTCCA CCAACTCTTT GGTTGAGAAA CTCTGAGCTA GAGACTCGAT 101

TTAACCGGCG AATTGGCCGC CAGTTTAGCC GTCAAATCGG CTTGTCCTTT GAACAGGAAA GTCACTAAAA CAGTGATTTT

GTACTGAAGT

CATGACTTCA

GTGGTGCTTT CACCACGAAA

GCTGCTGCCA CGACGACGGT ATTACCAGTG TAATGGTCAC CTCTAAATCA GAGATTTAGT AGACTAACTC TCTGATTGAG 201

GATAAGGCGC CTATTCCGCG ACTCAAGACG ATAGTTACCG TATCAATGGC TGAGTTCTGC TGCATGTCTT TCCGGGTTGG AGGCCCAACC ACGTACAGAA 251

GAACCTCGCT CTTGGAGCGA GGTTCGTGCA TACAGTCCAG ATGTCAGGTC CCAAGCACGT AGCGGTCGGA CTGAACGGGG GACTTGCCCC TCGCCAGCCT 301

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	AAACGCGGCC TTTGCGCCGG	
vectors (continued)	TACC CGGAACTGAG TGTCAGGCGT GGAATGAGAC AAACGCGGCC ATGG GCCTTGACTC ACAGTCCGCA CCTTACTCTG TTTGCGCCGG	
s and sequences of additional pCAL vector modules and pCAL vectors (continued)	TGTCAGGCGT	
ences of additional pCAL v	CGGAACTGAG GCCTTGACTC	
Figure 35a: Functional maps and seque	ACTGCCTACC TGACGGATGG	
Figure 35a:	351	

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401	ATAACAGCGG	AATGACACCG	GCGG AATGACACCG GTAAACCGAA AGGCAGGAAC AGGAGAGCGC	AGGCAGGAAC	AGGAGAGCGC
	TATTGTCGCC	TTACTGTGGC	CGCC TTACTGTGGC CATTTGGCTT TCCGTCCTTG TCCTCTCGCG	TCCGTCCTTG	TCCTCTCGCG
451	AGGAGGGAGC	CGCCAGGGGG	GAGC CGCCAGGGGG AAACGCCTGG TATCTTTATA GTCCTGTCGG	TATCTTTATA	GTCCTGTCGG

CAGGACAGCC	TTGTCAGGGG AACAGTCCCC
TCCTCCCTCG GCGGTCCCCC TTTGCGGACC ATAGAATAT CAGGACAGCC	TTTCGCCAC CACTGATTTG AGCGTCAGAT TTCGTGATGC TTGTCAGGGG
TTTGCGGACC	AGCGTCAGAT TCGCAGTCTA
GCGGTCCCCC	CACTGATTTG GTGACTAAAC
TCCTCCCTCG	GTTTCGCCAC
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г.	<b>~</b> 1
ACTTCCCTG1	TGAAGGGACF
GCCT ATGGAAAAC GGCTTTGCCG CGGCCCTCTC ACTTCCCTGT	CGGA TACCTTTTTG CCGAAACGGC GCCGGGAGAG TGAAGGGACA
GGCTTTGCCG	CCGAAACGGC
ATGGAAAAAC	TACCTTTTTG
GGCGGAGCCT	CCGCCTCGGA
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TTCGTAAGCC	AAGCATTCGG
AAT CTCCGCCCG	GAGGCGGGGC
TCT TCCAGGAAAT CTCCGCCCCG TTCGTA	AA GGACCGTAGA AGGTCCTTTA GAGGCGGGGC AAG
TAAGTATCTT CCTGGCATCT TCCAGGAA	GGACCGTAGA
TAAGTATCTT	ATTCATAGAA
601	

CAGTGAGCGA	SGCGAG CGGCGTCAGC TTGCTGGCTC GCATCGCTCA GTCACTCGCT
CGCTC GCCGCAGTCG AACGACCGAG CGTAGCGAGT CAGTGAGCGA	GCATCGCTCA
AACGACCGAG	TTGCTGGCTC
GCCGCAGTCG	CGGCGTCAGC
ATTTCCGCTC	TAAAGGCGAG
651	

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ACCGGTGCAG CTGCTGACGC

TGGCCACGTC GACGACTGCG

TAGTGTATAA

ATATAGGACA TATATCCTGT

CCTTCGCCTT GGAAGCGGAA

701

XmnI

ATCACATATT

AGTAGTCACG TCATCAGTGC

ACTGACACCC TGACTGTGGG

CTTCGTGAAG GAAGCACTTC

CCTGCCACAT GGACGGTGTA

GGAAAAAGA CCTTTTTCT

751

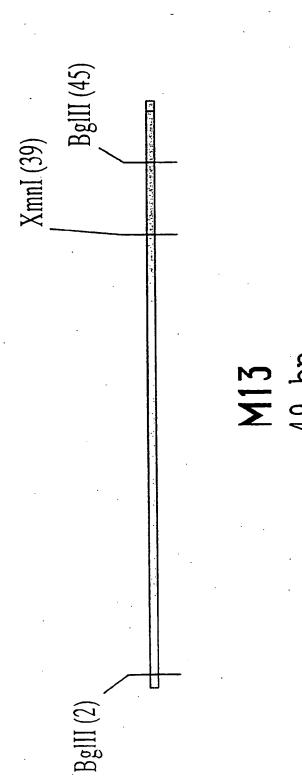
NheI

S CACTCCGCTA CAACATAGTA AGCCAGTATA

CG GTGAGGCGAT TCGGTCATAT GTTGTATCAT

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BglII

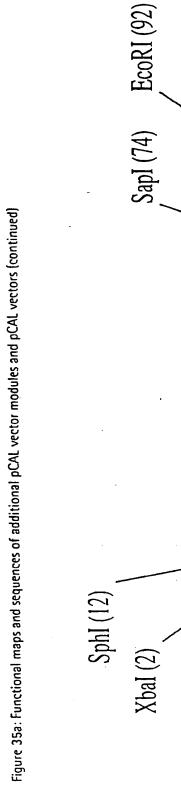
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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TTCAGATCT AAGTCTAGA ATGCTTCAAT TACGAAGTTA TACATACGAT ATGTATGCTA ACTTCGTATA TGAAGCATAT AGATCTCATA TCTAGAGTAT



**M19** 96 bp

M 19

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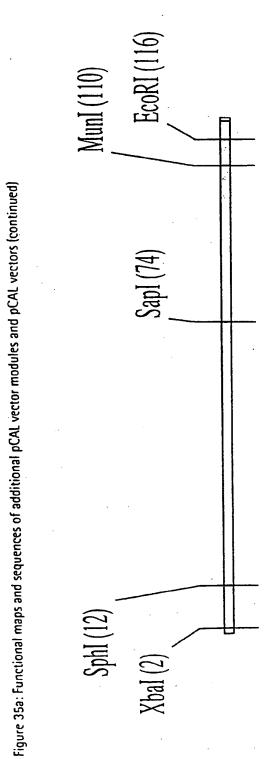
GATAACGTGA CTATTGCACT TTTGTTTCGT GCGTAGGAGA AAATAAAATG AAACAAAGCA CGCATCCTCT TTTATTTAC TCTAGAGCAT AGATCTCGTA

ECORI Sapi

GAATTC CTTAAG TACCAAAGCC ATGGTTTCGG CCGTTGCTCT TCACCCCTGT GGCAACGAGA AGTGGGGACA CCGTGAGAAT GGCACTCTTA

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**M20** 120 bp

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M 20:

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CTATTGCACT GATAACGTGA AAACAAAGCA TTTGTTTCGT AAATAAAATG TTTATTTAC GCGTAGGAGA CGCATCCTCT AGATCTCGTA TCTAGAGCAT

SapI

GACTACAAAG CTGATGTTTC ATGGTTTCGG TACCAAAGCC GGCAACGAGA AGTGGGGACA CCGTTGCTCT TCACCCCTGT CCGTGAGAAT GGCACTCTTA

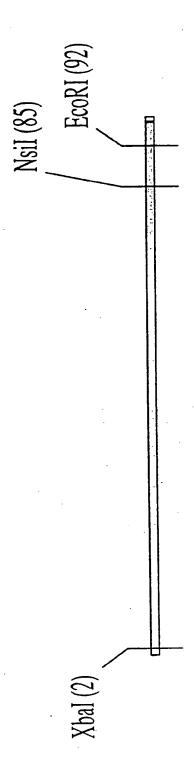
51

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TGAAGTGCA ATTGGAATTC

ATGAAGTGCA ATTGGAATTC TACTTCACGT TACCTTAAG

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**M21** 96 bp

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M 21:

XbaI

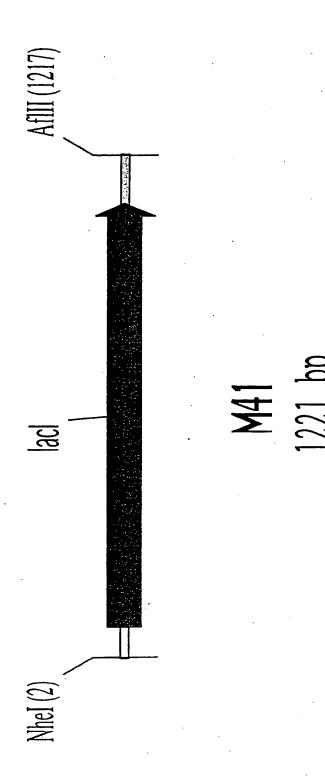
TICTICLIGC AAGAAGAACG TTATAGCGTA AATATCGCAT TATGAAAAAG ATACTTTTTC GAGGTGATTT CTCCACTAAA TCTAGAGGTT AGATCTCCAA

ECORI 2222 NsiI

CTTAAG GAATTC TIGCTACAAA IGCATACGCI AACGATGTTT ACGTATGCGA GTTTTTTCTA CAAAAAAGAT TAGATACAAG ATCTATGTTC

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## M 41:

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ATCAACTGGG TAGTTGACCC	TCTCGCGCCG AGAGCGCGGC	GGCGATTAAA	AAATTGTCGC TTTAACAGCG	GCGCCGTCGC	301
GGCCCTGCAC CCGGGACGTG	CCTCCAGTCT GGAGGTCAGA	GGCGTTGCCA CCGCAACGGT	GTTGCTGATT CAACGACTAA	GCAAACAGTC CGTTTGTCAG	251
CAACTGGCGG GTTGACCGCC	CGTGGCACAA GCACCGTGTT	TTCCTAACCG AAGGATTGGC	CTGAATTACA GACTTAATGT	GATGGCGGAG CTACCGCCTC	201
TGGAAGCGGC ACCTTCGCCG	CGGGAAAAAG GCCCTTTTTC	TGCGAAAACG ACGCTTTTGC	GCCACGTTTC CGGTGCAAAG	AACCAGGCCA TTGGTCCGGT	151
CCGCGTGGTG	AGACCGTTTC TCTGGCAAAG	GTCTCTTATC	GTATGCCGGT CATACGGCCA	ATGTCGCAGA TACAGCGTCT	101
ACGTTATACG TGCAATATGC	GAAACCAGTA CTTTGGTCAT	TGGTGAATGT ACCACTTACA	CAATTCAGGG GTTAAGTCCC	GGAAGAGAGT CCTTCTCTCA	51
GATAGCGCCC CTATCGCGGG	GGTATGGCAT CCATACCGTA	AACCTTTCGC TTGGAAAGCG	AATGGCGCAA TTACCGCGTT	GCTAGCATCG CGATCGTAGC	<b>~</b>

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

97/08320						PCT/I	EP96/03647
GAAGCCTGTA	GCTGATTATT	CTGCCTGCAC	CCCATCAACA	GGAGCATCTG	CATTAAGTTC	CTCACTCGCA	TGCCATGTCC
CTTCGGACAT	CGACTAATAA		GGGTAGTTGT	CCTCGTAGAC	GTAATTCAAG	GAGTGAGCGT	ACGGTACAGG
AAGCGGCGTC	GTGTCAGTGG	GCTGTGGAAG	TGACCAGACA	GACTGGGCGT	TTAGCTGGCC	GCATAAATAT	GCGACTGGAG
TTCGCCGCAG	CACAGTCACC	CGACACCTTC	ACTGGTCTGT	CTGACCCGCA	AATCGACCGG	CGTATTTATA	
TGGTAGAACG	CTCGCGCAAC	GGATGCTATT	TTGATGTCTC	GACGGTACGC	AATCGCGCTG	TGGCTGGCTG	GAACGGGAAG
ACCATCTTGC	GAGCGCGTTG	CCTACGATAA	AACTACAGAG	CTGCCATGCG	TTAGCGCGAC		CTTGCCCTTC
GTCGTGTCGA	GCACAATCTT	TGGATGACCA	GCGTTATTTC	CTCCCATGAG	GCCACCAGCA	CGTCTGCGTC	GCCGATAGCG
CAGCACAGCT	CGTGTTAGAA	ACCTACTGGT	CGCAATAAAG		CGGTGGTCGT	GCAGACGCAG	CGGCTATCGC
TGCCAGCGTG	AAGCGGCGGT TTCGCCGCCA	AACTATCCGC TTGATAGGCG	TAATGTTCCG ATTACAAGGC	GTATTATTT CATAATAAAA	GTCGCATTGG	TGTCTCGGCG	ATCAAATTCA TAGTTTAAGT
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GGAGGCCGTT GCGGGCAGTG AGGCTACCCG ATAAAAGCGG CTTCCTGACA 1151

GAAGGACTGT TATTTCGCC CGCCCGTCAC TCCGATGGGC

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GCCCACTTAA GCGGGTGAATT C TIGITITGCA GCCCACTIAA

1201

AACAAAACGT

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

Hind111 (994) Kbal (937) Sphl (957) 1pp-Terminator Ratll (886) lac p/o Pacl (1058) cat Bg111 (1) pCALO-1 2380 bp RNA! GenII-Nick ds-ori P15A origin Rgel (1641) Kmnl (1611) Ban11 (1398) **Agel (1965)** Nhel (1555)

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pCAL0-1:

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TTTTTTAAT AAAAAATTA TAACTGCCTT ATTGACGGAA CAGGCGTTTA AGGGCACCAA TCCCGTGGTT GTCCGCAAAT GATCTAGCAC CTAGATCGTG

AATTCGTAAG TTAAGCATTC TTGTAATTCA AACATTAAGT CGCAGTACTG GCGTCATGAC TGCCACTCAT ACGGTGAGTA 9990999909 51

GATGAACCTG CAAACGGCAT GAAGCCATCA TGCCGACATG

TATTTGCCCA CTACTTGGAC ATAAACGGGT GTTTGCCGTA TTGCGTATAA AACGCATATT GGAACAGCGG CCTTGTCGCC CTTCGGTAGT ACGGCTGTAC GGCATCAGCA CCGTAGTCGT

TTAGCGGTCG

ATCACTTTTG

TAGTGAAAAC

AATCGCCAGC

AAACTGGTGA TTTGACCACT GTTTAAATCA CAAATTTAGT TATTGGCTAC ATAACCGATG AAGTTGTCCA TTCAACAGGT GGGGCGAAG CCCCCCTTC 201

TTATTTGGGA AATAAACCCT ACATATTCTC TGTATAAGAG GAGACGAAAA CTCTGCTTTT GGGATTGGCT CCCTAACCGA AACTCACCCA TTGAGTGGGT 251

CTTGCGAATA GAACGCTTAT AGGCCAGGTT TTCACCGTAA CACGCCACAT GTGCGGTGTA AAGTGGCATT TCCGGTCCAA TTAGGGAAAT AATCCCTTTA 301

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	351		AACTGCCGGA	AATCGTCGTG	GTATTCACTC	CAGAGCGATG	
		ATACACATCT	TTGACGGCCT	TTAGCAGCAC	CATAAGTGAG	GTCTCGCTAC	
•	401	AAAACGTTTC TTTTGCAAAG	AGTTTGCTCA TCAAACGAGT	TGGAAAACGG ACCTTTTGCC	TGTAACAAGG ACATTGTTCC	GTGAACACTA CACTTGTGAT	
	451	TCCCATATCA AGGGTATAGT	CCAGCTCACC GGTCGAGTGG	GTCTTTCATT CAGAAAGTAA	GCCATACGGA CGGTATGCCT	ACTCCGGGTG TGAGGCCCAC	
SUBSTIT	501	AGCATTCATC TCGTAAGTAG	AGGCGGGCAA TCCGCCCGTT	GAATGTGAAT CTTACACTTA	AAAGGCCGGA TTTCCGGCCT	TAAAACTTGT ATTTTGAACA	
UTE SHEET	551	GCTTATTTTT CGAATAAAAA	CTTTACGGTC GAAATGCCAG	TTTAAAAAGG AAATTTTTCC	CCGTAATATC GGCATTATAG	CAGCTGAACG GTCGACTTGC	
(RULE 26)	601	GTCTGGTTAT CAGACCAATA	AGGTACATTG TCCATGTAAC	AGCAACTGAC TCGTTGACTG	TGAAATGCCT ACTTTACGGA	CAAAATGTTC GTTTTACAAG	
	651	TTTACGATGC AAATGCTACG	CATTGGGATA GTAACCCTAT	TATCAACGGT ATAGTTGCCA	GGTATATCCA CCATATAGGT	GTGATTTTTT CACTAAAAAA	
	701	TCTCCATTTT AGAGGTAAAA	AGCTTCCTTA TCGAAGGAAT	GCTCCTGAAA CGAGGACTTT	ATCTCGATAA TAGAGCTATT	CTCAAAAAAT GAGTTTTTTA	

	AACCT
ntinued)	TGAAAGTTGG AACCT
ules and pCAL vectors (co	TTCATTATGG
Iditional pCAL vector mod	GTGATCTTAT
nal maps and sequences of additional pCAL vector modules and pCAL vectors (continued)	ACCCCCGGTA GTGATCTTAT TTCATTATGG TGAAAGTTGG AACCT
Figure 35a: Functiona	751

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AACCTCACCC TTGGAGTGGG	GCTTTACACT CGAAATGTGA	ATAACAATTT TATTGTTAAA	ACCCCCCCC TGGGGGGGGG	HindIII ~~~~~~ ATAAGCTTGA TATTCGAACT	TTTGTCTGCC AAACAGACGG
TGAAAGTTGG ACTTTCAACC	GGCACCCCAG	TTGTGAGCGG	xbaI ~~~~~ GAATTTCTAG CTTAAAGATC	ATACGAAGTT TATGCTTCAA	CGACATTTTT GCTGTAAAAA
TTCATTATGG AAGTAATACC	TCACTCATTA AGTGAGTAAT	TTGTGTGGAA	CCATGATTAC GGTACTAATG	AATGTACGCT TTACATGCGA	GCAGATTGTG CGTCTAACAC
GTGATCTTAT CACTAGAATA	GTGAGTTAGC CACTCAATCG	GGCTCGTATG CCGAGCATAC	ACAGCTATGA TGTCGATACT	AACTTCGTAT TTGAAGCATA	GAAAAATGGC CTTTTTACCG
ACGCCCGGTA	Aatii ~~~~~~ GACGTCTAAT CTGCAGATTA	TTATGCTTCC AATACGAAGG	CACACAGGAA GTGTGTCCTT	SphI ~~~~~~ CGCATGCCAT GCGTACGGTA	CCTGTGAAGT GGACACTTCA
751	801	851	901	951	1001

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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r gracatgaaa a cargracttr	TTGTTAAATC AACAATTTAG	CTTATAAATC GAATATTTAG	TGGAACAAGA ACCTTGTTCT	AAAAACCGTC TTTTGGCAG	CAAGTTTTTT GTTCAAAAAA	BanII ~~~~~ GGGAGCCCCC CCCTCGGGGG
GGGGGGGGGT	CGTTAAATTT GCAATTTAAA	GGCAAAATCC CCGTTTTAGG	TGTTCCAGTT ACAAGGTCAA	TCAAAGGGCG AGTTTCCCGC	TCACCCTAAT AGTGGGATTA	CACTAAATCG GAACCCTAAA GTGATTTAGC CTTGGGATTT
GGGCCGGCCT	TTAAAATTCG AATTTTAAGC	GGCCGAAATC CCGGCTTTAG	GGTTGAGTGT CCAACTCACA	GACTCCAACG CTGAGGTTGC	ACGAGAACCA TGCTCTTGGT	CACTAAATCG
AGGGGGGGGG	TAATATTTTG ATTATAAAAC	TTAACCAATA AATTGGTTAT	ACCGAGATAG TGGCTCTATC	AAAGAACGTG TTTCTTGCAC	TATCAGGGCG ATGGCCCACT ATAGTCCCGC TACCGGGTGA	GGGGTCGAGG TGCCGTAAAG CCCCAGCTCC ACGGCATTTC
CAAATTAA CAAATTAA	TTGTAAACGT AACATTTGCA	AGCTCATTTT TCGAGTAAAA	AAAAGAATAG TTTTCTTATC	GTCCACTATT CAGGTGATAA	TATCAGGGCG	GGGGTCGAGG
1051	1101	1151	1201	1251	1301	1351
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1401	GATTTAGAGC CTAAATCTCG	TTGACGGGGA	AAGCCGGCGA TTCGGCCGCT	ACGTGGCGAG TGCACCGCTC	AAAGGAAGGG TTTCCTTCCC
1451	AAGAAAGCGA TTCTTTCGCT	AAGGAGCGGG TTCCTCGCCC	CGCTAGGGCG GCGATCCCGC	CTGGCAAGTG GACCGTTCAC	TAGCGGTCAC ATCGCCAGTG
1501	GCTGCGCGTA CGACGCGCAT	ACCACCACAC TGGTGGTGTG	CCGCCGCGCT	TAATGCGCCG	CTACAGGGCG
1551.	Nhel ~~~~~ CGTGCTAGCG GCACGATCGC	GAGTGTATAC	TGGCTTACTA	TGTTGGCACT	GATGAGGGTG
					AgeI
1601	TCAGTGAAGT GAGT GAGT GAGT GAGT GAGTCACTTCA	GCTTCATGTG	GCAGGAGAAA CGTCCTCTTT	AAAGGCTGCA TTTCCGACGT	CCGGTGCGTC GGCCACGCAG
1651	AGCAGAATAT TCGTCTTATA	GTGATACAGG CACTATGTCC	ATATATTCCG TATATAAGGC	CTTCCTCGCT	CACTGACTCG GTGACTGAGC
1701	CTACGCTCGG	TCGTTCGACT	GCGGCGAGCG	GAAATGGCTT	ACGAACGGGG

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TTCAGTCCGA CCGCTGCGCC TTATCCGGTA AAGTCAGGCT GGCGACGCGG AATAGGCCAT

CTGTATGCAC GAACCCCCCG GACATACGTG CTTGGGGGGC

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	TGCTTGCCCC
and personal many and seguences of additional pCAL vector modules and pCAL vectors (continued)	Higure 35al: Functional maps and separation and page page CGCCGCTCGC CTTTACCGAA TGCTTGCCCC

TGCTTGCCCC	GAAGTGAGAG CTTCACTCTC	GACAAGCATC CTGTTCGTAG	AGGACTATAA TCCTGATATT	CTCCTGTTCC GAGGACAAGG	CGTTTGTCTC GCAAACAGAG CCAAGCTGGA GGTTCGACCT
CTTTACCGAA	ACTTAACAGG TGAATTGTCC	CCGCCCCCT	GAAACCCGAC CTTTGGGCTG	CTCCTGCGCT GAGGACGCGA	GTTATGGCCG CAATACCGGC GCAGTTCGCT CGTCAAGCGA
CGCCGCTCGC	CCAGGAAGAT GGTCCTTCTA	TCCATAGGCT AGGTATCCGA	CAGTGGTGGC GTCACCACCG	TGGCGGCTCC ACCGCCGAGG	TCATTCCGCT AGTAAGGCGA TTCCGGGTAG
SCAAGCTGA	CTGGAAGATG GACCTTCTAC	AAGCCGTTTT TTCGGCAAAA	ACGCTCAAAT TGCGAGTTTA	CGTTTCCCCC	AgeI ~~~~~~ TTTACCGGTG AAATGGCCAC TGACACTCAG
gure 35a: Functional maps and sequences of accounting the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the	CGGAGATTTC GCCTCTAAAG	GGCCGCGGCA	ACGAAATCTG TGCTTTAGAC	AGATACCAGG TCTATGGTCC	TGCCTTTCGG ACGGAAAGCC ATTCCACGCC TAAGGTGCGG
sa: Functional	1751	1801	1851	1901	1951
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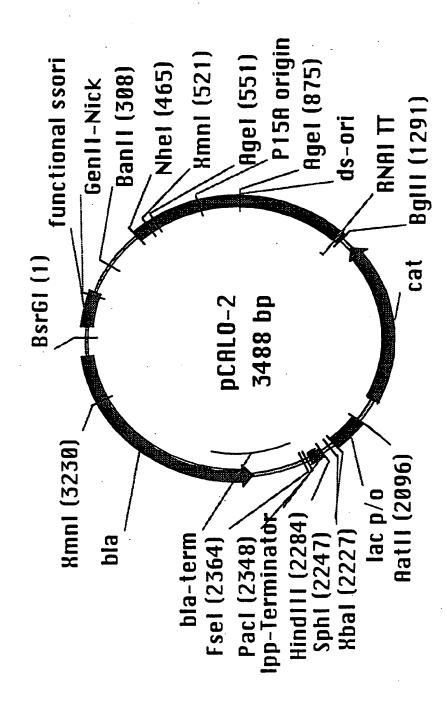
CAAAACGATC TCAAGAAGAT CATCTTATTA GTTTTGCTAG AGTTCTTCTA GTAGAATAAT

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

		Bglii				Æ 26)
ACGCGCAGAC TGCGCGTCTG	CGTTTTCAGA GCAAGAGATT ACGCGCAGAC GCAAAAGTCT CGTTCTCTAA TGCGCGTCTG	CGTTTTCAGA GCAAAAGTCT	GCCCTGCAAG GCGGTTTTTT CGGGACGTTC CGCCAAAAA	GCCCTGCAAG	2301	SHEET (RUL
ACGAAAAACC TGCTTTTTGG	CAGTTACCTC GGTTCAAAGA GTTGGTAGCT CAGAGAACCT ACGAAAACC GTCAATGGAG CCAAGTTTCT CAACCATCGA GTCTCTTGGA TGCTTTTTGG	GTTGGTAGCT CAACCATCGA	GGTTCAAAGA CCAAGTTTCT	CAGTTACCTC	2251	UBSTITUTE
TCCTCCAAGC AGGAGGTTCG	TA AACTGAAAGG ACAAGTTTTA GTGACTGCGC TCCTCCAAGC	ACAAGTTTTA TGTTCAAAAT	AACTGAAAGG TTGACTTTCC	GTTAAGGCTA CAATTCCGAT	2201	S
TCATGCGCCG AGTACGCGGC	TAGAGGAGTT AGTCTTGAAG TCATGCGCCG ATCTCCTCAA TCAGAACTTC AGTACGCGGC	TAGAGGAGTT ATCTCCTCAA	GTAATTGATT CATTAACTAA	GCAGCCACTG	2151	
ACCACTGGCA TGGTGACCGT	TGAGTCCAAC CCGGAAAGAC ATGCAAAAGC ACCACTGGCA ACTCAGGTTG GGCCTTTCTG TACGTTTTCG TGGTGACCGT	CCGGAAAGAC GGCCTTTCTG	ACTATCGTCT TGAGTCCAAC TGATAGCAGA ACTCAGGTTG	ACTATCGTCT TGATAGCAGA	2101	

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

pCAL0-2:

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GCAATTTAAA CGTTAAATTT AATTTTAAGC TTAAAATTCG ATTATAAAAC TAATATTTTG AACATTTGCA TTGTAAACGT CATGTACTTT GTACATGAAA

CCGTTTTAGG GGCAAAATCC CCGGCTTTAG GGCCGAAATC TTAACCAATA AATTGGTTAT TCGAGTAAAA AGCTCATTTT AACAATTTAG TTGTTAAATC 51

ACAAGGTCAA TGTTCCAGTT CCAACTCACA GGTTGAGTGT ACCGAGATAG TGGCTCTATC TTTTCTTATC AAAAGAATAG CTTATAAATC SAATATTAG 101

AGTTTCCCGC TCAAAGGGCG GACTCCAACG CTGAGGTTGC AAAGAACGTG TTTCTTGCAC GTCCACTATT CAGGTGATAA TGGAACAAGA ACCTTGTTCT 151

TCACCCTAAT AGTGGGATTA ATGGCCCACT ACGAGAACCA TGCTCTTGGT TACCGGGTGA TATCAGGGCG ATAGTCCCGC AAAAACCGTC TTTTGGCAG 201

GAACCCTAAA CTTGGGATTT CACTAAATCG GTGATTTAGC TGCCGTAAAG ACGGCATTTC GGGGTCGAGG CCCCAGCTCC CAAGTTTTTT GTTCAAAAA 251

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? ? ? ? TIGACGGGA AAGCCGGCGA ACGIGGCGAG GGGAGCCCCC GATTTAGAGC 301

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ninued) TTCGGCCGCT TGCACCGCTC	CGCTAGGGCG CTGGCAAGTG GCGATCCCGC GACCGTTCAC	CCGCCGCGCT TAATGCGCCG GGCGCGCGA ATTACGCGGC	TGGCTTACTA TGTTGGCACT ACCGAATGAT ACAACCGTGA	AgeI	GCAGGAGAAA AAAGGCTGCA CGTCCTCTTT TTTCCGACGT	ATATATTCCG CTTCCTCGCT TATATAAGGC GAAGGAGCGA	GCGGCGAGCG GAAATGGCTT
of additional pCAL vector modules and pCAL vectors (continued) 3G CTAAAATCTCG AACTGCCCCT TTC	AAGAAAGCGA AAGGAGCGGG C TTCTTTCGCT TTCCTCGCCC G	GCTGCGCGTA ACCACCACAC C	Nhel CGTGCTAGCG GAGTGTATAC T GCACGATCGC CTCACATATG A	XmnI	TCAGTGAAGT GCTTCATGTG GAGTCACTTCA CGAAGTACAC C	AGCAGAATAT GTGATACAGG TCGTCTTATA CACTATGTCC	CTACGCTCGG TCGTTCGACT (
Figure 35a: Functional maps and sequences of add	AAAGGAAGGG	TAGCGGTCAC	CTACAGGGCG		GATGAGGGTG	AgeI ~~~~~ CCGGTGCGTC GGCCACGCAG	CACTGACTCG
Figure 35a: Functiona	351	401	16. The state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of t	SHEET 5 / 204	(RULE 26)	551	601

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CTTTACCGAA	ACTTAACAGG TGAATTGTCC	CCGCCCCCCT	GAAACCCGAC CTTTGGGCTG	CTCCTGCGCT GAGGACGCGA	GTTATGGCCG	GCAGTTCGCT CGTCAAGCGA	CCGCTGCGCC
ntinued) CGCCGCTCGC	CCAGGAAGAT GGTCCTTCTA	TCCATAGGCT AGGTATCCGA	CAGTGGTGGC GTCACCACCG	TGGCGGCTCC	TCATTCCGCT AGTAAGGCGA	TTCCGGGTAG AAGGCCCATC	TTCAGTCCGA AAGTCAGGCT
ules and pCAL vectors (co	CTGGAAGATG GACCTTCTAC	AAGCCGTTTT TTCGGCAAAA	ACGCTCAAAT TGCGAGTTTA	CGTTTCCCCC	AgeI ~~~~~~ TTTACCGGTG AAATGGCCAC	TGACACTCAG ACTGTGAGTC	GAACCCCCCG
ditional pCAL vector mod GATGCGAGCC	CGGAGATTTC GCCTCTAAAG	GGCCGCGGCA	ACGAAATCTG TGCTTTAGAC	AGATACCAGG TCTATGGTCC	TGCCTTTCGG ACGGAAAGCC	ATTCCACGCC TAAGGTGCGG	CTGTATGCAC GACATACGTG
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued) GTGACTGAGC GATGCGAGCC AGCAAGCTGA CGC	ACGAACGGGG TGCTTGCCCC	GAAGTGAGAG CTTCACTCTC	GACAAGCATC CTGTTCGTAG	AGGACTATAA TCCTGATATT	CTCCTGTTCC GAGGACAAGG	CGTTTGTCTC GCAAACAGAG	CCAAGCTGGA
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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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ATGCAAAAGC TACGTTTTCG	AGTCTTGAAG TCAGAACTTC	GTGACTGCGC CACTGACGCG	CAGAGAACCT GTCTCTTGGA	GCAAGAGATT. CGTTCTCTAA	BglII	A GATCTAGCAC T CTAGATCGTG	AAAAAATTA CGCCCGCCC TTTTTTAAT GCGGGGGGGG
CCGGAAAGAC GGCCTTTCTG	TAGAGGAGTT ATCTCCTCAA	ACAAGTTTTA TGTTCAAAAT	GTTGGTAGCT CAACCATCGA	CGTTTTCAGA GCAAAAGTCT		CATCTTATTA	
TGAGTCCAAC ACTCAGGTTG	GTAATTGATT CATTAACTAA	AACTGAAAGG TTGACTTTCC	GGTTCAAAGA CCAAGTTTCT	GCGGTTTTTT CGCCAAAAAA		TCAAGAAGAT AGTTCTTCTA	TAACTGCCTT ATTGACGGAA
ACTATCGTCT TGATAGCAGA	GCAGCCACTG	GTTAAGGCTA CAATTCCGAT	CAGTTACCTC GTCAATGGAG	GCCCTGCAAG CGGGACGTTC		CAAAACGATC GTTTTGCTAG	AGGGCACCAA
TTATCCGGTA AATAGGCCAT	ACCACTGGCA TGGTGACCGT	TCATGCGCCG AGTACGCGGC	TCCTCCAAGC AGGAGGTTCG	ACGAAAAACC TGCTTTTTGG		ACGCGCAGAC TGCGCGTCTG	CAGGCGTTTA GTCCGCAAAT
1001	1051	1101	1151	1201		1251	1301
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TGCCGACATG ACGGCTGTAC	GGCATCAGCA CCGTAGTCGT	GGGGCGAAG CCCCCGCTTC	AACTCACCCA TTGAGTGGGT	TTAGGGAAAT AATCCCTTTA	TATGTGTAGA ATACACATCT	AAAACGTTTC TTTTGCAAAG	TCCCATATCA AGGGTATAGT
ntinued) TTAAGCATTC AATTCGTAAG	AATCGCCAGC TTAGCGGTCG	TAGTGAAAAC ATCACTTTTG	AAACTGGTGA TTTGACCACT	AATAAACCCT TTATTTGGGA	CTTGCGAATA GAACGCTTAT	CAGAGCGATG GTCTCGCTAC	GTGAACACTA CACTTGTGAT
ules and pCAL vectors (col TTGTAATTCA AACATTAAGT	GATGAACCTG CTACTTGGAC	TATTTGCCCA ATAAACGGGT	GTTTAAATCA CAAATTTAGT	ACATATTCTC TGTATAAGAG	CACGCCACAT	GTATTCACTC CATAAGTGAG	TGTAACAAGG ACATTGTTCC
ditional pCAL vector mod CGCAGTACTG GCGTCATGAC	CAAACGGCAT GTTTGCCGTA	TTGCGTATAA AACGCATATT	TATTGGCTAC ATAACCGATG	GAGACGAAAA CTCTGCTTTT	TTCACCGTAA AAGTGGCATT	AATCGTCGTG TTAGCAGCAC	TGGAAAACGG ACCTTTTGCC
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued) 1351 TGCCACTCAT CGCAGTACTG TTGTAATTCA TTA ACGGTGAGTA GCGTCATGAC AACATTAAGT AAT	GAAGCCATCA CTTCGGTAGT	CCTTGTCGCC GGAACÀGCGG	AAGTTGTCCA TTCAACAGGT	GGGATTGGCT CCCTAACCGA	AGGCCAGGTT TCCGGTCCAA	AACTGCCGGA TTGACGGCCT	AGTTTGCTCA TCAAACGAGT
e 35a: Functional 1351	1401	1451	1501	TEST 1521	1601	1651	1701
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ATC FAG	LTT	rat ata	rgc Acg	TTT	GTA	AAT ITA	ICC
AGCATTCATC TCGTAAGTAG	GCTTATTTT CGAATAAAAA	GTCTGGTTAT CAGACCAATA	TTTACGATGC AAATGCTACG	TCTCCATTTT AGAGGTAAAA	ACGCCCGGTA TGCGGGCCAT	Aatii ~~~~~ GACGTCTAAT CTGCAGATTA	TTATGCTTCC
AGC	GCJ CG <b>Z</b>	GTC	TTT AAA	TC:	AC( TG(	A CTC	TT.
antinued) ACTCCGGGTG TGAGGCCCAC	TAAAACTTGT ATTTTGAACA	CAGCTGAACG GTCGACTTGC	CAAAATGTTC GTTTTACAAG	GTGATTTTTT CACTAAAAAA	CTCAAAAAT GAGTTTTTTA	AACCTCACCC TTGGAGTGGG	GCTTTACACT
ules and pCAL vectors (co GCCATACGGA CGGTATGCCT	AAAGGCCGGA TTTCCGGCCT	CCGTAATATC GGCATTATAG	TGAAATGCCT ACTTTACGGA	GGTATATCCA CCATATAGGT	ATCTCGATAA TAGAGCTATT	TGAAAGTTGG ACTTTCAACC	GGCACCCCAG
ditional pCAL vector mod GTCTTTCATT CAGAAAGTAA	GAATGTGAAT CTTACACTTA	TTTAAAAAGG AAATTTTTCC	AGCAACTGAC TCGTTGACTG	TATCAACGGT ATAGTTGCCA	GCTCCTGAAA CGAGGACTTT	TTCATTATGG AAGTAATACC	TCACTCATTA
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued) 1751 CCAGCTCACC GTCTTTCATT GCCATACGGA ACT GGTCGAGTGG CAGAAAGTAA CGGTATGCCT TGA	AGGCGGGCAA TCCGCCCGTT	CTTTACGGTC GAAATGCCAG	AGGTACATTG TCCATGTAAC	CATTGGGATA GTAACCCTAT	AGCTTCCTTA TCGAAGGAAT	GTGATCTTAT	GTGAGTTAGC
5a: Functional 1751	1801	1851	1901	1951	2001	2051	2101
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CAAATTAATT

AAACAGACGG

GCTGTAAAAA

CGTCTAACAC

CTTTTTACCG

	AATACGAAGG
gure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)	CACTCAATCG AGTGAGTAAT CCGTGGGGTC CGAAATGTGA AATACGAAGG
Figure 3!	

CACACAGGAA GTGTGTCCTT TATTGTTAAA ATAACAATTT AACACTCGCC TTGTGAGCGG AACACACCTT TTGTGTGGAA CCGAGCATAC GGCTCGTATG 2151

SphI XbaI

GCGTACGGTA CGCATGCCAT TGGGGGGGG GAATITCTAG ACCCCCCCC CTTAAAGATC GGTACTAATG CCATGATTAC TGTCGATACT ACAGCTATGA 2201

HindIII

CCTGTGAAGT ATAAGCTTGA ATACGAAGTT AATGTACGCT AACTTCGTAT 2251

GGACACTTCA GTTTAATTAA PacI TATTCGAACT TTTGTCTGCC TATGCTTCAA CGACATTTTT TTACATGCGA GCAGATTGTG GAAAAATGGC TTGAAGCATA 2301

AGGAAACTAG TCCTTTGATC CTCAAGAAGA GAGTTCTTCT CAAAAAGGAT GTTTTTCCTA CGGCCATTAT GCCGGTAATA FseI 5000000000 2351

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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

	2401	TTTTCTACGG AAAAGATGCC	GGTCTGACGC CCAGACTGCG	TCAGTGGAAC AGTCACCTTG	GAAACTCAC CTTTTGAGTG	GTTAAGGGAT CAATTCCCTA	
	2451	TTTGGTCATG AAACCAGTAC	AGATTATCAA TCTAATAGTT	AAAGGATCTT TTTCCTAGAA	CACCTAGATC GTGGATCTAG	CTTTTAAATT GAAAATTTAA	
S	2501	AAAAATGAAG TTTTTACTTC	TTTTAAA.TCA AAAATTTAGT	ATCTAAAGTA TAGATTTCAT	TATATGAGTA ATATACTCAT	AACTTGGTCT TTGAACCAGA	
UBSTITUTE	2551	GACAGTTACC CTGTCAATGG	CAATGCTTAA GTTACGAATT	TCAGTGAGGC AGTCACTCCG	ACCTATCTCA TGGATAGAGT	GCGATCTGTC CGCTAGACAG	
SHEET (RUI	2601	TATTTCGTTC ATAAAGCAAG	ATCCATAGTT TAGGTATCAA	GCCTGACTCC CGGACTGAGG	CCGTCGTGTA GGCAGCACAT	GATAACTACG CTATTGATGC	
LE 26)	2651	ATACGGGAGG TATGCCCTCC	GCTTACCATC CGAATGGTAG	TGGCCCCAGT	GCTGCAATGA CGACGTTACT	TACCGCGAGA	
	2701	CCCACGCTCA	CCGGCTCCAG	ATTTATCAGC TAAATAGTCG	AATAAACCAG TTATTTGGTC	CCAGCCGGAA GGTCGGCCTT	
	2751	GGGCCGAGCG	CAGAAGTGGT	CCTGCAACTT GGACGTTGAA	TATCCGCCTC ATAGGCGGAG	CATCCAGTCT GTAGGTCAGA	

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

AATTATCAAA	CGCTCGTCGT GCGAGCAGCA	GCGAGTTACA	GTCCTCCGAT CAGGAGGCTA	GTTATGGCAG CAATACCGTC	CTTTTCTGTG	TGCGGCGACC	CCACATAGCA GGTGTATCGT
TCAAGCGGTC	CGTGGTGTCA GCACCACAGT	AACGATCAAG TTGCTAGTTC	AGCTCCTTCG TCGAGGAAGC	ATCACTCATG TAGTGAGTAC	CCGTAAGATG GGCATTCTAC	GAATAGTGTA CTTATCACAT	TAATACCGCG ATTATGGCGC
TAGAGTAAGT ATCTCATTCA	CTACAGGCAT GATGTCCGTA	TCCGGTTCCC	AAAAGCGGTT TTTTCGCCAA	CCGCAGTGTT GGCGTCACAA	GTCATGCCAT	GTCATTCTGA CAGTAAGACT	CAATACGGGA GTTATGCCCT
GCCGGGAAGC CGGCCCTTCG	GTTGCCATTG CAACGGTAAC	TTCATTCAGC AAGTAAGTCG	TGTTGTGCAA ACAACACGTT	AGTAAGTTGG TCATTCAACC	TTCTCTTACT AAGAGAATGA	ACTCAACCAA TGAGTTGGTT	TGCCCGGCGT ACGGGCCGCA
ATTAACTGTT TAATTGACAA	GCGCAACGTT CGCGTTGCAA	TTGGTATGGC AACCATACCG	TGATCCCCCA	CGTTGTCAGA GCAACAGTCT	CACTGCATAA GTGACGTATT	ACTGGTGAGT TGACCACTCA	GAGTTGCTCT CTCAACGAGA
2801	2851	2901	2951	3001	3051	3101	3151
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Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

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GCGAAAACTC CGCTTTTGAG	CCACTCGCGC GGTGAGCGCG	TCTGGGTGAG AGACCCACTC
GAACTTTAAA AGTGCTCATC ATTGGAAAAC GTTCTTCGGG GCGAAAACTC CTTGAAATTT TCACGAGTAG TAACCTTTTG CAAGAAGCCC CGCTTTTGAG	CT TACCGCTGTT GAGATCCAGT TCGATGTAAC CCACTCGCGCGAA ATGGCGACAA CTCTAGGTCA AGCTACATTG GGTGAGCGCG	GA TCCTCAGCAT CTTTTACTTT CACCAGCGTT TCTGGGTGAG CT AGGAGTCGTA GAAAATGAAA GTGGTCGCAA AGACCCACTC
GAACTTTAAA AGTGCTCATC ATTGGAAAAC GTTCTTCGGG CTTGAAATTT TCACGAGTAG TAACCTTTTG CAAGAAGCCC	GAGATCCAGT CTCTAGGTCA	CTTTTACTTT GAAAATGAAA
AGTGCTCATC TCACGAGTAG	TACCGCTGTT ATGGCGACAA	TCCTCAGCAT AGGAGTCGTA
GAACTTTAAA CTTGAAATTT	TCAAGGATCT AGTTCCTAGA	ACCCAACTGA
3201	3251	3301
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## BsrGI

GTTATAATAA

AAATGTTGAA TACTCATACT CTTCCTTTTT CAATATTATT

3401

TTTACAACTT ATGAGTATGA GAAGGAAAAA

GAAGCATTTA

GGCGACACGG

TCCCTTATTC

AAGGCAAAAT GCCGCAAAAA AGGGAATAAG

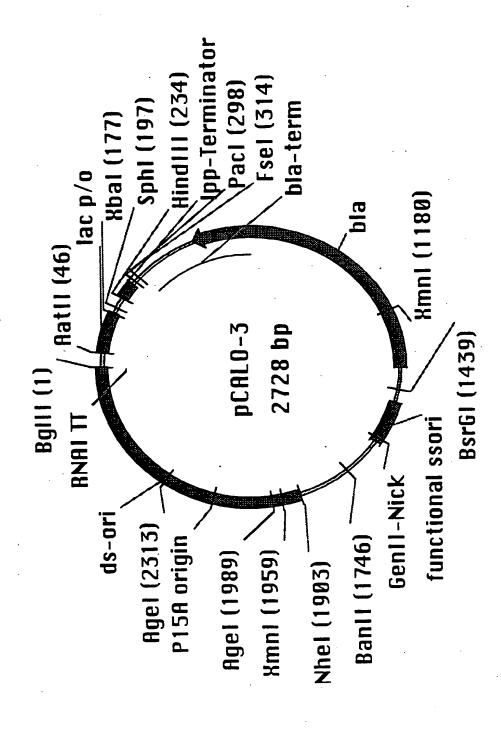
TICCGTTTTA CGGCGTTTTT

GTTTTTGTCC

CAAAAACAGG

## ATTTGAAT TAAACTTA TCAGGGTTAT TGTCTCATGA GCGGATACAT CGCCTATGTA ACAGAGTACT AGTCCCAATA 3451

SUBSTITUTE SHEET (RULE 28 173 / 204



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PacI

AatII

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

				PC1/EP96/030
CACGTCTAAT CTGCAGATTA	TTATGCTTCC AATACGAAGG	CACACAGGAA GTGTGTCCTT	SphI ~~~~~ CGCATGCCAT GCGTACGGTA	CCTGTGAAGT GGACACTTCA
ACGAAGTTAT TGCTTCAATA	GCTTTACACT CGAAATGTGA	ATAACAATTT TATTGTTAAA	ACCCCCCC TGGGGGGGGG	HindIII ~~~~~~ ATAAGCTTGA TATTCGAACT
TGTATGCTAT ACATACGATA	GGCACCCCAG CCGTGGGGGTC	TTGTGAGCGG	XbaI ~~~~~~ GAATTTCTAG A CTTAAAGATC I	ATACGAAGTT TATGCTTCAA
CTTCGTATAA GAAGCATATT	TCACTCATTA AGTGAGTAAT	TTGTGTGGAA AACACACCTT	CCATGATTAC GGTACTAATG	AATGTACGCT TTACATGCGA
GATCTCATAA CTAGAGTATT	GTGAGTTAGC CACTCAATCG	GGCTCGTATG	ACAGCTATGA TGTCGATACT	AACTTCGTAT
←	51	101	151	201

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TTGAACCAGA

AACTTGGTCT

TATATGAGTA

TTTTAAATCA ATCTAAAGTA

AAAAATGAAG TTTTTACTTC

451

ATATACTCAT

TAGATTTCAT

AAAATTTAGT

GAAAATTTAA

GTGGATCTAG

TTTCCTAGAA

AAAGGATCTT

AGATTATCAA

TTTGGTCATG

AAACCAGTAC

TCTAATAGTT

CACCTAGATC

CTTTTAAATT

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

251	GAAAAATGGC CTTTTTACCG	GCAGATTGTG CGTCTAACAC	c gcagattgtg cgacattttt tttgtctgcc gtttaattaa g cgtctaacac gctgtaaaaa aaacagacgg caaattaatt	TTTGTCTGCC	GTTTTAATTTAA CAAATTAATT	
	R	FseI				
,		日本日日ないこうこう	~~~~~~~ 	なじをなじななしよう		
3 O T	9000000000	GCCGGTAATA	CCCCCCCCCC GCCGGTAATA GTTTTCCTA GAGTTCTTCT AGGAAACTAG	GAGTTCTTCT	AGGAAACTAG	
351	TTTTCTACGG	GGTCTGACGC	G GGTCTGACGC TCAGTGGAAC GAAAACTCAC GTTAAGGGAT	GAAAACTCAC	GTTAAGGGAT	
 	AAAAGATGCC	CCAGACTGCG	AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTTGAGTG CAATTCCCTA	CTTTTGAGTG	CAATTCCCTA	

CGCTAGACAG GATAACTACG CTATTGATGC GCGATCTGTC ACCTATCTCA TGGATAGAGT CCGTCGTGTA GGCAGCACAT CAATGCTTAA TCAGTGAGGC GCCTGACTCC CGGACTGAGG AGTCACTCCG GTTACGAATT ATCCATAGTT TAGGTATCAA TATTTCGTTC ATAAAGCAAG GACAGTTACC CTGTCAATGG 501 551

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GTTATGGCAG

CCGCAGTGTT ATCACTCATG

CGTTGTCAGA AGTAAGTTGG

951

CAATACCGTC

TAGTGAGTAC

GGCGTCACAA

TCATTCAACC

GCAACAGTCT

GTCCTCCGAT

TCGAGGAAGC

TGTTGTGCAA AAAAGCGGTT AGCTCCTTCG

TTTTCGCCAA

ACAACACGTT

TGATCCCCCA ACTAGGGGGGT

	TACCGCGAGA ATGGCGCTCT	CCAGCCGGAA GGTCGGCCTT	CATCCAGTCT GTAGGTCAGA	TTAATAGTTT AATTATCAAA	CGCTCGTCGT GCGAGCAGCA	GCGAGTTACA CGCTCAATGT
	GCTGCAATGA T CGACGTTACT A	AATAAACCAG C TTATTTGGTC G	TATCCGCCTC C ATAGGCGGAG G	AGTTCGCCAG T TCAAGCGGTC A	CGTGGTGTCA C	AACGATCAAG G TTGCTAGTTC C
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)	TGGCCCCAGT ACCGGGGTCA	ATTTATCAGC TAAATAGTCG	CCTGCAACTT	TAGAGTAAGT ATCTCATTCA	CTACAGGCAT	TCCGGTTCCC AGGCCAAGGG
ditional pCAL vector mod	GCTTACCATC CGAATGGTAG	CCGGCTCCAG	CAGAAGTGGT GTCTTCACCA	GCCGGGAAGC CGGCCCTTCG	GTTGCCATTG CAACGGTAAC	TTCATTCAGC AAGTAAGTCG
maps and sequences of ad	ATACGGGAGG TATGCCCTCC	CCCACGCTCA GGGTGCGAGT	GGGCCGAGCG CCCGGCTCGC	ATTAACTGTT TAATTGACAA	GCGCAACGTT	TTGGTATGGC AACCATACCG
ı: Functional	601	651	701	751	801	851
Figure 35a		-			TE SHEET (P. 177 / 204	ULE 26)

AAATGTTGAA TACTCATACT CTTCCTTTTT CAATATTATT GAAGCATTTA

TGTG	GACC	AGCA		ACTC	52525	TGAG	ACGG
CTTTTCTGTG	TGCGGCGACC ACGCCGCTGG	CCACATAGCA GGTGTATCGT		GCGAAAACTC CGCTTTTGAG	CCACTCGCGC GGTGAGCGCG	TCTGGGTGAG	GGCGACACGG CCGCTGTGCC
ntinued) CCGTAAGATG GGCATTCTAC	GAATAGTGTA CTTATCACAT	TAATACCGCG ATTATGGCGC	2	GTTCTTCGGG CAAGAAGCCC	TCGATGTAAC	CACCAGCGTT GTGGTCGCAA	AGGGAATAAG TCCCTTATTC
ences of additional pCAL vector modules and pCAL vectors (continued) ATAA TTCTCTTACT GTCATGCCAT CCG' TATT AAGAGAATGA CAGTACGGTA GGC	GTCATTCTGA CAGTAAGACT	CAATACGGGA GTTATGCCCT	IrmX	ATTGGAAAAC TAACCTTTTG	GAGATCCAGT CTCTAGGTCA	CTTTTACTTT GAAAATGAAA	GCCGCAAAAA CGGCGTTTTT
ditional pCAL vector mod TTCTCTTACT AAGAGAATGA	ACTCAACCAA TGAGTTGGTT	TGCCCGGCGT		AGTGCTCATC TCACGAGTAG	TACCGCTGTT ATGGCGACAA	TCCTCAGCAT AGGAGTCGTA	AAGGCAAAAT TTCCGTTTTA
Figure 35a: Functional maps and sequences of ad 1001 CACTGCATAA GTGACGTATT	ACTGGTGAGT TGACCACTCA	GAGTTGCTCT CTCAACGAGA		GAACTTTAAA CTTGAAATTT	TCAAGGATCT AGTTCCTAGA	ACCCAACTGA TGGGTTGACT	CAAAAACAGG GTTTTTGTCC
5a: Functional 1001	1051	11.01		1151	1201	1251	1301
gure 3			SUB		EET (RULE 2	26)	
ιĒ				178 / 20	)4		

BanII

TTTACAACTT ATGAGTATGA GAAGGAAAAA GTTATAATAA CTTCGTAAAT Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

BsrGI

ACATGAAATT TGTACTTTAA TAAACTTACA ATTTGAATGT CGCCTATGTA GCGGATACAT ACAGAGTACT TGTCTCATGA AGTCCCAATA TCAGGGTTAT 1401

GTTAAATCAG CAATTTAGTC AATTTAAAAA TTAAATTTTT TTTTAAGCGC AAAATTCGCG ATATTTTGTT GTAAACGTTA 1451

TATAAAACAA CATTTGCAAT

TATAAATCAA ATATTTAGTT GTTTTAGGGA CAAAATCCCT CCGAAATCGG GGCTTTAGCC AACCAATAGG TTGGTTATCC CTCATTTTT GAGTAAAAA 1501

GAACAAGAGT CTTGTTCTCA TTCCAGTTTG AAGGTCAAAC TTGAGTGTTG AACTCACAAC CGAGATAGGG GCTCTATCCC TTCTTATCTG AAGAATAGAC 1551

AAACCGTCTA TTTGGCAGAT AAAGGGCGAA TTTCCCGCTT CTCCAACGTC GAGGTTGCAG AGAACGTGGA TCTTGCACCT CCACTATTAA GGTGATAATT 1601

AGTTTTTGG TCAAAAAACC ACCCTAATCA GAGAACCATC GGCCCACTAC TCAGGGCGAT 1651

TGGGATTAGT CTCTTGGTAG CCGGGTGATG AGTCCCGCTA

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GAGCCCCCGA	AGGAAGGGAA TCCTTCCCTT	GCGGTCACGC CGCCAGTGCG	ACAGGGGGGG TGTCCCGCGC	TGAGGGTGTC ACTCCCACAG		GGTGCGTCAG CCACGCAGTC	CTGACTCGCT GACTGAGCGA
GAG(	AGG/ TCC	3000 0000	ACA( TGT(		eI ~~~~		
ntinued) ACCCTAAAGG TGGGATTTCC	GTGGCGAGAA CACCGCTCTT	GGCAAGTGTA CCGTTCACAT	ATGCGCCGCT _TACGCGGCGA	TTGGCACTGA	AgeI	AGGCTGCACC TCCGACGTGG	TCCTCGCTCA
ules and pCAL vectors (co CTAAATCGGA GATTTAGCCT	GCCGGCGAAC CGGCCGCTTG	CTAGGGCGCT GATCCCGCGA	GCCGCGCTTA	GCTTACTATG CGAATGATAC		AGGAGAAAAA TCCTCTTTTTT	ATATTCCGCT TATAAGGCGA
iditional pCAL vector mod CCGTAAAGCA GGCATTTCGT	GACGGGGAAA CTGCCCCTTT	GGAGCGGGCG CCTCGCCCGC	CACCACACCC GTGGTGTGGG	GTGTATACTG CACATATGAC		TTCATGTGGC	GATACAGGAT CTATGTCCTA
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued) 1701 GGTCGAGGTG CCGTAAAGCA CTAAATCGGA ACCO	TTTAGAGCTT AAATCTCGAA	GAAAGCGAAA CTTTCGCTTT	TGCGCGTAAC ACGCGCATTG	NheI ~~~~~~ TGCTAGCGGA ACGATCGCCT	ImmX		CAGAATATGT GTCTTATACA
a: Functional 1701	1751	1801	1851	1901		1951	2001
Figure 35	SUBSTITUTE SHEET (RULE 26) 180 / 204						

Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued)

					1/21 90/030
AGTGAGAGGG TCACTCTCCC	CAAGCATCAC GTTCGTAGTG	GACTATAAAG CTGATATTTC	CCTGTTCCTG GGACAAGGAC	TTTGTCTCAT	AAGCTGGACT TTCGACCTGA
TTAACAGGGA AATTGTCCCT	GCCCCCTGA CGGGGGGACT	AACCCGACAG TTGGGCTGTC	CCTGCGCTCT GGACGCGAGA	TATGGCCGCG	AGTTCGCTCC TCAAGCGAGG
AGGAAGATAC TCCTTCTATG	CATAGGCTCC GTATCCGAGG	GTGGTGGCGA	GCGGCTCCCT	ATTCCGCTGT	CCGGGTAGGC
GGAAGATGCC CCTTCTACGG	GCCGTTTTTC CGGCAAAAAG	GCTCAAATCA CGAGTTTAGT	TTTCCCCCTG	Agel ~~~~~~ TACCGGTGTC ATGGCCACAG	ACACTCAGTT TGTGAGTCAA
GAGATTTCCT CTCTAAAGGA	CCGCGGCAAA GGCGCCGTTT	GAAATCTGAC CTTTAGACTG	ATACCAGGCG TATGGTCCGC	CCTTTCGGTT GGAAAGCCAA	TCCACGCCTG AGGTGCGGAC
2101	2151	2201	2251	2301	2351
	GAGATTTCCT GGAAGATGCC AGGAAGATAC TTAACAGGGA CTCTAAAGGA CCTTCTACGG TCCTTCTATG AATTGTCCCT	GAGATTTCCT GGAAGATGCC AGGAAGATAC TTAACAGGGA CTCTAAAGGA CCTTCTACGG TCCTTCTATG AATTGTCCCT CCGCGGCAAA GCCGTTTTTC CATAGGCTCC GCCCCCTGA GGCGCCGTTT CGGCAAAAG GTATCCGAGG CGGGGGGACT	GAGATTTCCT GGAAGATGCC AGGAAGATAC TTAACAGGGA CTCTAAAGGA CCTTCTACGG TCCTTCTATG AATTGTCCCT CCGCGGCAAA GCCGTTTTTC CATAGGCTCC GCCCCCTGA GGCGCCGTTT CGGCAAAAAG GTATCCGAGG CGGGGGGACT GAAATCTGAC GCTCAAATCA GTGGTGGCGA AACCCGACAG CTTTAGACTG CGAGTTTAGT CACCACCGCT TTGGGCTGTC	GAGATTTCCT GGAAGATGCC AGGAAGATAC TTAACAGGGA CTCTAAAGGA CCTTCTACGG TCCTTCTATG AATTGTCCCT CCGCGGCAAA GCCGTTTTTC CATAGGCTCC GCCCCCCTGA GGCGCCCGTTT CGGCAAAAAG GTATCCGAGG CGGGGGACT GAAATCTGAC GCTCAAATCA GTGGTGGCGA AACCCGACAG CTTTAGACTG CGAGTTTAGT CACCACCGCT TTGGGCTGTC ATACCAGGCG TTTCCCCCTG GCGCCTCCTT CCTGCGCTCT TATGGTCCGC AAAGGGGGAC CGCCGAGGA GGACGCGAGA	GAGATTTCCT GGAAGATGCC AGGAAGATAC TTAACAGGGA CTCTTAAAGG TCCTTCTATG AATTGTCCCT GGCGCCCTTTTTC CATAGGCTCC GCCCCCTGA GGCGCCCTTTTTTC CATAGGCTCC GCCCCCTGA GGCGCCCTTTTAGATCA GTGGTGGCGA AACCCGACAG CTTTAGACTG CGAGTTTAGT CACCACCGCT TTGGGCTGTC TTGGGCTGTC TATGGTCCGC AAGGGGGAC CGCCGAGGGA GGACGCGAGA GGACGCGAGA GGACGCGAGA GGACGCGAGA GGACGCGGGGGAC TATGGTCCGC AAGGGGGAC CGCCGAGGGA GGACGCGGGGGAC AAGGCCACAG TAAGGCCACAG TAAGGCCGCG GGAAAGCCAA ATGGCCACAG TAAGGCGACA ATACCGGCGC GGAAAGCCAA ATGGCCACAG TAAGGCGACA ATACCGGCGC

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ATCCGGTAAC TAGGCCATTG	CACTGGCAGC GTGACCGTCG	ATGCGCCGGT TACGCGGCCA	CTCCAAGCCA GAGGTTCGGT	GAAAAACCGC CTTTTTGGCG	GCGCAGACCA		
SCGCCTT	GCAAAAGCAC C CGTTTTCGTG G	TCTTGAAGTC A AGAACTTCAG I	GACTGCGCTC C		AAGAGATTAC C TTCTCTAATG C		
Figure 35a: Functional maps and sequences of additional pCAL vector modules and pCAL vectors (continued) 2401 GTATGCACGA ACCCCCGTT CAGTCCGACC GCT(CAC) CATACGTGCT TGGGGGGCCAA GTCAGGCTGG CGA(CAC)	GGAAAGACAT CCTTTCTGTA	GAGGAGTTAG	AAGTTTTAGT TTCAAAATCA	TGGTAGCTCA GAGAACCTAC ACCATCGAGT CTCTTGGATG	TTTTCAGAGC AAAAGTCTCG	Bglii	TCTTATTA AGAATAAT
ditional pCAL vector modi ACCCCCCGTT TGGGGGGCCAA	AGTCCAACCC TCAGGTTGGG	AATTGATTTA TTAACTAAAT	CTGAAAGGAC GACTTTCCTG	TTCAAAGAGT AAGTTTCTCA	GGTTTTTTCG CCAAAAAAGC		AAGAAGATCA TTCTTCTAGT
maps and sequences of ad GTATGCACGA CATACGTGCT	TATCGTCTTG ATAGCAGAAC	AGCCACTGGT TCGGTGACCA	TAAGGCTAAA ATTCCGATTT	GTTACCTCGG	CCTGCAAGGC GGACGTTCCG		AAACGATCTC TTTGCTAGAG
Figure 35a: Functional $2401$	2451	2501		709 JTE SHEET ( 182 / 204	2651 (95 TE 20		2701

Figure 35b: List of oligonucleotides used for synthesis of modules

M1: PCR using template

NoVspAatII: TAGACGTC

M2: synthesis

BloxA-A: TATGAGATCTCATAACTTCGTATAATGTACGCTATACG-

AAGTTAT

BloxA-B: TAATAACTTCGTATAGCATACATTATACGAAGTTATG-

**AGATCTCA** 

M3: PCR, NoVspAatII as second oligo

XloxS-muta: CATTTTTGCCCTCGTTATCTACGCATGCGATAACTTCGTA-

TAGCGTACATTATACGAAGTTATTCTAGACATGGTCATAGCTGTTTCCTG

M7-I: PCR

gIIINEW-fow: GGGGGGAATTCGGTGGTGGTGGATCTGCGTGCGCTG-

**AAACGGTTGAAAGTTG** 

gIIINEW-rev: CCCCCCAAGCTTATCAAGACTCCTTATTACG

M7-II: PCR

glllss-fow: GGGGGGGAATTCGGAGGCGGTTCCGGTGGTGGC

M7-III: PCR

glllsupernew-fow: GGGGGGGGAATTCGAGCAGAAGCTGATCTCT-

GAGGAGGATCTGTAGGGTGGTGGCTCTGGTTCCGGTGATTTTG

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Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M8: synthesis

Iox514-A: CCATAACTTCGTATAATGTACGCTATACGAAGTTATA

lox514-B: AGCTTATAACTTCGTATAGCGTACATTATACGAAGT-

**TATGGCATG** 

M9II: synthesis

M9II-fow: AGCTTGACCTGTGAAGTGAAAAATGGCGCAGATT-

M9II-rev: GTACACCCCCCCAGGCCGGCCCCCCCCCCTTTAA-

TTAAACGGCAGACAAAAAAAAATGTCGCACAATCTGCG

M10II: assembly PCR with template

bla-fow: GGGGGGGTGTACATTCAAATATGTATCCGCTCATG

bla-seq4: GGGTTACATCGAACTGGATCTC

bla1-muta: CCAGTTCGATGTAACCCACTCGCGCACCCAACTGATC-

CTCAGCATCTTTTACTTTCACC

blall-muta: ACTCTAGCTTCCCGGCAACAGTTAATAGACTGGATG-

GAGGCGG

bla-NEW: CTGTTGCCGGGAAGCTAGAGTAAG

bla-rev: CCCCCCTTAATTAAGGGGGGGGGCCGGCCATTATCAAA-

AAGGATCTCAAGAAGATCC

M11II/III: PCR, site-directed mutagenesis

Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

f1-fow: GGGGGGGCTAGCACGCCCCTGTAGCGGCGCATTAA

f1-rev: CCCCCCCTGTACATGAAATTGTAAACGTTAATATTTTG

f1-t133.muta: GGGCGATGGCCCACTACGAGAACCATCACCCTAATC

M12: assembly PCR using template

p15-fow: GGGGGGAGATCTAATAAGATGATCTTCTTGAG

p15-NEWI: GAGTTGGTAGCTCAGAGAACCTACGAAAAACCGCCCTG-

**CAAGGCG** 

p15-NEWII: GTAGGTTCTCTGAGCTACCAACTC

p15-NEWIII: GTTTCCCCCTGGCGCTCCCTCCTGCGCTCTCCTGTTCCT-

GCC

p15-NEWIV: AGGAGGGAGCCGCCAGGGGGAAAC

p15-rev: GACATCAGCGCTAGCGGAGTGTATAC

M13: synthesis

BloxXB-A: GATCTCATAACTTCGTATAATGTATGCTATACGAAGTTA-

TTCA

BloxXB-B: GATCTGAATAACTTCGTATAGCATACATTATACGAAGTTA-

**TGAGA** 

M14-Ext2: PCR, site-directed mutagenesis

ColeXT2-fow: GGGGGGGAGATCTGACCAAAATCCCTTAACGTGAG

Col-mutal: GGTATCTGCGCTCTGCTGTAGCCAGTTACCTTCGG

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Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

Col-rev: CCCCCCGCTAGCCATGTGAGCAAAAGGCCAGCAA

M17: assembly PCR using template

CAT-1: GGGACGTCGGGTGAGGTTCCAAC

CAT-2: CCATACGGAACTCCGGGTGAGÇATTCATC

CAT-3: CCGGAGTTCCGTATGG

CAT-4: ACGTTTAAATCAAAACTGG

CAT-5: CCAGTTTTGATTTAAACGTAGCCAATATGGACAACTTCTTC-

GCCCCGTTTTCACTATGGGCAAATATT

CAT-6: GGAAGATCTAGCACCAGGCGTTTAAG

M41: assembly PCR using template

LAC1: GAGGCCGGCCATCGAATGGCGCAAAAC

LAC2: CGCGTACCGTCCTCATGGGAGAAAATAATAC

LAC3: CCATGAGGACGGTACGCGACTGGGCGTGGAGCATCTGGTCGCA-

TTGGGTCACCAGCAAATCCGCTGTTAGCTGGCCCATTAAG

LAC4: GTCAGCGGCGGGATATAACATGAGCTGTCCTCGGTATCGTCG

LAC5: GTTATATCCCGCCGCTGACCACCATCAAAC

LAC6: CATCAGTGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGT4TTG-

**GGAGCCAGGGTGGTTTTTC** 

LAC7: GGTTAATTAACCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCC-

AGCTGCATCAGTGAATCGGCCAAC

M41-MCS-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGCTT-

AAGGGGGGGGGGG

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Figure 35b: List of oligonucleotides used for synthesis of modules (continued)

M41-MCS-rev: CTAGCCCCCCCCCCCTTAAGCCCCCCCCGGTCCGGT-

TTAAACACTAGT

M41-fow: CTAGACTAGTGTTTAAACCGGACCGGGGGGGGGGCTTAA-

GGGGGGGGGGG

M41-rev: CCCCCCTTAAGTGGGCTGCAAAACAAAACGGCCTCC-

TGTCAGGAAGCCGCTTTTATCGGGTAGCCTCACTGCCCGCTTTCC

M41-A2: GTTGTTGTGCCACGCGGTTAGGAATGTAATTCAGCTCCGC

M41-B1: AACCGCGTGGCACAACAAC

M41-B2: CTTCGTTCTACCATCGACACGACCACGCTGGCACCCAGTTG

M41-C1: GTGTCGATGGTAGAACGAAG

M41-CII: CCACAGCAATAGCATCCTGGTCATCCAGCGGATAGTT-

AATAATCAGCCCACTGACACGTTGCGCGAG

M41-DI: GACCAGGATGCTATTGCTGTGG

M41-DII: CAGCGCGATTTGCTGGTGGCCCAATGCGACCAGATGC

M41-EI: CACCAGCAAATCGCGCTG

M41-EII: CCCGGACTCGGTAATGGCACGCATTGCGCCCAGCGCC

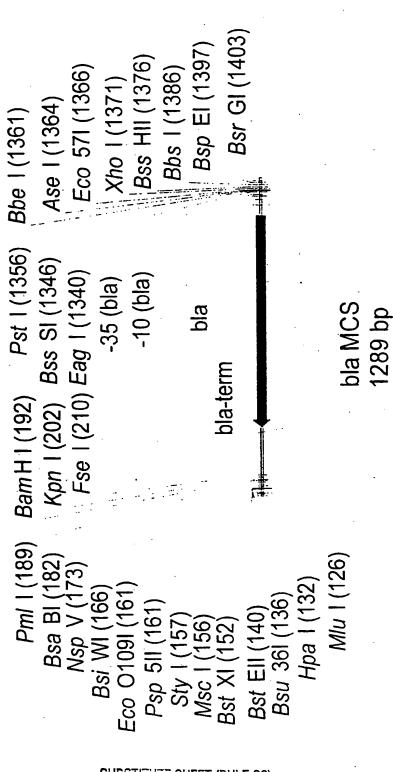
M41-FI: GCCATTACCGAGTCCGGG

M42: synthesis

Eco-H5-Hind-fow: AATTCCACCATCACCATTGACGTCTA

Eco-H5-Hind-rev: AGCTTAGACGTCAATGGTGATGATGGTGG

Figure 36: functional map and sequence of ß-lactamase-MCS module



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TTTTCCTAGA

CTCTAATAGT

GCAATTCCCT AAAACCAGTA

GCTTTTGAGT

StyI

Figure 36: functional map and sequence of B-lactamase-MCS module (continued)

					BsiwI NspV	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	GTACGTTCGA	CATGCAAGCT
2 2 2 2 2 2	Psp511	~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	Eco01091	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	H		AAGCCCCTGG CCAAGGTCCC GTACGTTCGA	TTCGGGGACC GGTTCCAGGG CATGCAAGCT
			BstXI	~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	MscI	? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?	AAGCCCCTGG	TTCGGGGACC
			Bsu36I	~~~	BstEII	? ? ? ? ?	CGCGTTAACC TCAGGTGACC	TTGG AGTCCACTGG
			MluI Bsu	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	HpaI	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	CGCGTTAACC	GCGCAATTGG
							126	

	**************************************	CGGTACCAGG CCGGCCATTA TCAAAAAGGA	GCCATGGTCC GGCCGGTAAT AGTTTTTCCT	SAAG ATCCTTTGAT CTTTTCTACG GGGTCTGACG CTCAGTGGAA	CTTC TAGGAAACTA GAAAAGATGC CCCAGACTGC GAGTCACCTT		CGAAAACTCA CGTTAAGGGA TTTTGGTCAT GAGATTATCA AAAAGGATCT
FseI	<pre></pre>		ວລວອອ	GGGTC	CCCAG	,	GAGAT
KpnI		CGGTACCAGG	GCCATGGTCC	 CTTTTCTACG	GAAAAGATGC		TTTTGGTCAT
BamHI	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	CCAT CACGTGGATC	GGTA GTGCACCTAG	ATCCTTTGAT	TAGGAAACTA		CGTTAAGGGA
NspVBsaBI	2 1 2 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	AGATTACCAT	TCTAATGGTA	TCTCAAGAAG	AGAGTTCTTC		CGAAAACTCA
		176		226			2,16

PmlI

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ATCTCATTCA

CGGCCCTTCG

TAATTGACAA

GTAGGTCAGA

ATAGGCGGAG

CTACAGGCAT GATGTCCGTA

CAACGGTAAC

CGCGTTGCAA

AATTATCAAA

TCAAGCGGTC

919

AGTICGCCAG TIAAIAGITT GCGCAACGIT GITGCCATIG

## Figure 36: functional map and sequence of B-lactamase-MCS module (continued)

AATCTAAAGT TTAGATTTCA	TCAGTGAGGC AGTCACTCCG	GCCTGACTCC CGGACTGAGG	TGGCCCCCAGT ACCGGGGTCA	ATTTATCAGC TAAATAGTCG	CCTGCAACTT GGACGTTGAA	TAGAGTAAGT
GTTTTAAATC CAAAATTTAG	CAATGCTTAA GTTACGAATT	ATCCATAGTT TAGGTATCAA	GCTTACCATC CGAATGGTAG	CCGGCTCCAG	CAGAAGTGGT GTCTTCACCA	GCCGGGAAGC
TAAAAATGAA ATTTTTACTT	TGACAGTTAC ACTGTCAATG	TATTTCGTTC ATAAAGCAAG	ATACGGGAGG TATGCCCTCC	CCCACGCTCA GGGTGCGAGT	GGGCCGAGCG	ATTAACTGTT
CCTTTTAAAT GGAAAATTTA	AAACTTGGTC TTTGAACCAG	GCGATCTGTC CGCTAGACAG	GATAACTACG CTATTGATGC	TACCGCGAGA ATGGCGCTCT	CCAGCCGGAA GGTCGGCCTT	CATCCAGTCT
TCACCTAGAT AGTGGATCTA	ATATATGAGT TATATACTCA	ACCTATCTCA TGGATAGAGT	CCGTCGTGTA GGCAGCACAT	GCTGCAATGA CGACGTTACT	AATAAACCAG TTATTTGGTC	TATCCGCCTC
326	376	426	476	526	576	929
		5	SUBSTITUTE	SHEET (RUI	LE 26)	

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GTTCTTCGGG GCGAAAACTC TCAAGGATCT TACCGCTGTT GAGATCCAGT CAAGAAGCCC CGCTTTTGAG AGTTCCTAGA ATGGCGACAA CTCTAGGTCA

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Figure 36: functional
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TCCGGTTCCC	AAAAGCGGTT	CCGCAGTGTT	GTCATGCCAT	GTCATTCTGA	CAATACGGGA	ATTGGAAAAC
	TTTTCGCCAA	GGCGTCACAA	CAGTACGGTA	CAGTAAGACT	GTTATGCCCT	TAACCTTTTG
TTCATTCAGC	TGTTGTGCAA	AGTAAGTTGG	TTCTCTTACT	ACTCAACCAA	TGCCCGGCGT	AGTGCTCATC
AAGTAAGTCG	ACAACACGTT	TCATTCAACC	AAGAGAATGA	TGAGTTGGTT	ACGGGCCGCA	TCACGAGTAG
TTGGTATGGC	TGATCCCCCA	CGTTGTCAGA	CACTGCATAA	ACTGGTGAGT	GAGTTGCTCT	GAACTTTAAA
AACCATACCG	ACTAGGGGGT	GCAACAGTCT	GTGACGTATT	TGACCACTCA	CTCAACGAGA	CTTGAAATTT
CGCTCGTCGT GCGAGCAGCA	GCGAGTTACA	GTCCTCCGAT	GTTATGGCAG CAATACCGTC	CTTTTCTGTG GAAAAGACAC	TGCGGCGACC	CCACATAGCA GGTGTATCGT
CGTGGTGTCA	AACGATCAAG	AGCTCCTTCG	ATCACTCATG	CCGTAAGATG	GAATAGTGTA	TAATACCGCG
	TTGCTAGTTC	TCGAGGAAGC	TAGTGAGTAC	GGCATTCTAC	CTTATCACAT	ATTATGGCGC
726	176	8 8 8	9 L 8 UBSTITUTE	SHEET (RUL	9 L 6 . E 26)	1026
		•			•	

(continued)
ICS module
gure 36: functional map and sequence of B-lactamase-MCS module (continued
s of B-
g sednence
тар апс
functional
gure 36: f
Ē

1126	TCGATGTAAC AGCTACATTG	CCACTCGTGC GGTGAGCACG BSSSI	ACCCAACTGA TGGGTTGACT	TCTTCAGCAT AGAAGTCGTA Eco57I	CTTTTACTTT GAAAATGAAA
1176	CACCAGCGTT GTGGTCGCAA	TCTGGGTGAG	CAAAAACAGG GTTTTTGTCC	AAGGCAAAAT TTCCGTTTTA	GCCGCAAAAA CGGCGTTTTT
1226	AGGGAATAAG TCCCTTATTC	GGCGACACGG AAATGTTGAA CCGCTGTGCC TTTACAACTT	AAATGTTGAA TTTACAACTT	TACTCATACT ATGAGTATGA	CTTCCTTTTT GAAGGAAAAA
1276	CAATATTATT GTTATAATAA	GAAGCATTTA CTTCGTAAAT	TCAGGGTTAT AGTCCCAATA	TGTCTCATGA ACAGAGTACT	GCGGATACAT CGCCTATGTA
			PstI		XhoI
		Eagl	BssSI	Bbel Asel	I BSSHII
1326	ATTTGAATGT TAAACTTACA	ACTCGGCCGC TGAGCCGGCG	ACGAGCTGCA	GGCGCCATTA CCGCGGTAAT	ATGGCTCGA( TACCGAGCT
	BSSHII		BspEI BsrGI	H ?	

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GTACTTTAA CATGAAATT GCGAAACAGA AGGCCTACAT CGCTTTGTCT TCCGGATGTA Figure 36: functional map and sequence of B-lactamase-MCS module (continued) BbsI CGCGCTTCAG Eco57I 1376

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WO 97/08320 PCT/EP96/03647

Figure 37: Oligo and primer design for Vκ CDR3 libraries

		<del>-</del>									10							
O_K3L_5	5'-	G	С	C	C	T	G	C	Α	Α	G	C	G[G]	Α	Α	G	Α	C
															Bt	sl		
														E			D	
Vk1 & Vk3	5'-	G	C	C	C	T	G	C	Α	À	G	C	GG	A	Α	G	Α	C
			•											Ε			D	•
Vk2	5'-	G	Ċ	C	Ċ	T	G	C	Α	Α	G	C	GG	Α	Α	G	Α	C
								_						Ε			D	
Vk4	5'-	G	C	C	C	T	G	C	Α	Α	G	C	GG	Α	Α	G	Α	C

PCT/EP96/03647

Figure 37: Oligo and primer design for  $V\kappa$  CDR3 libraries

-3<sub>,</sub> 20 30 40

F A TV Y Y C Q
T T T G C G A C T T A T T A T T G C C A

V G V Y Y C
G T G G G C G T G T A T T A T T G C C A

V A V Y C
G T G G C G G G T G T A T T A T T G C C A

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PCT/EP96/03647

Figure 37: Oligo and primer design for  $V\kappa$  CDR3 libraries

50

9

3'- G G A

G

T A C C T

G

ACCT

G

T A C C T

																•	
G	C	T	********						G	С	T				G	С	Τ
G		Τ	G	Α	T	G	Α	T	G	Α	Τ				G	Α	T
G	Α	G							G	Α	G				G	Α	G
T	T	T							T	T	T				T	T	T
G	G	T	G	G	T	G	G	T	_	G	Ţ				G	G	T
C	Α	T					•••		С	Α	Τ				С	Α	T
Α		T							Α	T	Τ				Α	T	T
A	Α	G			•				Α	Α	G				Α	Α	G
C	T	T							С	T	Τ				С	T	T
Α	T	G			******				Α	T	G				Α	T	G
Α	Α	T	Α	Α	T	Α	Α	T			T				Α		T
					•••••				С	C	T	C	С	T	С		T
C	Α	G	ļ		·				С	Α	G	·			С		G
C	G	T							С	G	Τ				С	G	T
T	С	T	T	C	T	Τ	С	T	T	C	T	Τ	C	T	T	C	T
A	C	T			•••••				Α	C	T				Α	С	T
G	T	T			••••••				G	T	T				G	T	T
T	G	G	-		******				Τ	G	G				Τ	G	G
T	Α	T	T	Α	T				T	Α	T				Τ	Α	Τ
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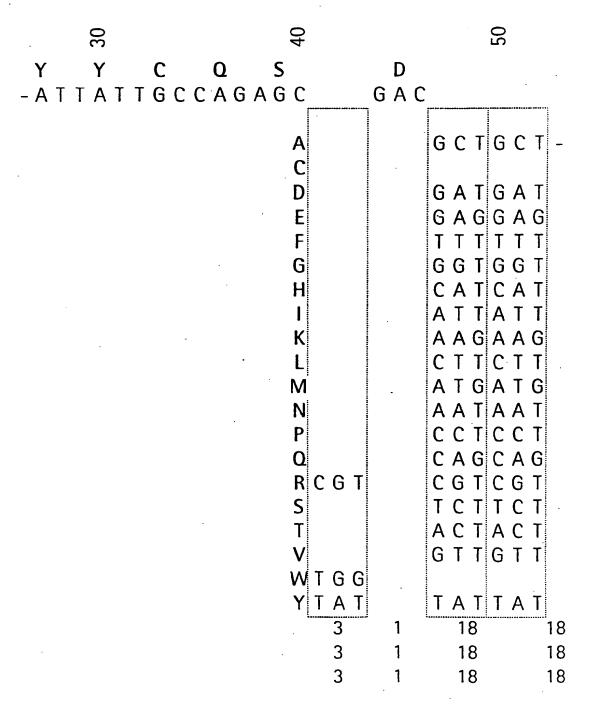
				20										80	81			
A	A C	C	G	G	T	Α	Α	G	C	Τ	T	Ţ	C	G	G	-5'	0_K3	3L_3
Γ		M	scl					•										
F		G	_		0											- •		
T	T G	G	C	C	A	T	T	C	G	Α	Α	A	G	С	C	-3'		
F		G			Q												-	
T	T G	G	С	С	Α	T	Ţ	C	G	A	A	A	G	C	C	-3'		
F		G			Q													
T	TG	G	C	С	Α	T	T	C	G	Α	Α	A	G	C	C	-3'		





Figure 38: Oligo and primer design for Vλ CDR3 libraries

Figure 38: Oligo and primer design for VA CDR3 libraries



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Figure 38: Oligo and primer design for VA CDR3 libraries

G G G T K L
GGCGGCGGCACGAAGTTA

				_		:	g	_	:				
-	G	C	T	G	C	Τ	G	C	T	G	C	T	
	G	Α	T	G	Α	Τ	G	Α	T	G	Α	T	
	G	Α	G	G	Α	G	G	Α	G	G	Α	G	
	T	T	T	T	T	T	T	T	T	T	T	T	
	G	G	T	G	G	T	G	G	T	G	G	T	
	C	Α	T	C	Α	T	C	Α	T	C	Α	T	
	Α	T	T	Α	T	T	Α	T	T	Α	T	T	
	Α	Α	G	Α	Α	G	Α	.A	G	Α	Α	G	
	C	T	T	С	T	T	С	T	T	C	T	· T	
	Α	T	G	Α	T	G	Α	Ţ	G	Α	T	G	
	Α	Α	T	Α	Α	T	Α	Α	T	Α	Α	Ţ	•
	C	C	T	С	C	T	C	C	T	C	C	T	
	C	Α	G	C	Α	G	С	A	G	C	Α	G	
	C	G	T	С	G	T	С	G	T	C	G	T	
	T	C	T	Τ	C	T	Τ	C	T	Τ	C	T	
	Α	C	T	Α	C	T	Α	C	T	Α	C	T	•
	G	T	T	G	T	T	G	T	T	G	T	T	•
										T	G	G	ì
	Т	Α	T	T	Α	T	T	Α	. T	Т	Α	. T	Variability
		18	3	.i	•••••				****		19	)	3.32E+05
		18	3		18	3					19	}	5.98E+06
		18	3		18	3		18	3		19	9	1.08E+08

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Figure 38: Oligo and primer design for VA CDR3 libraries

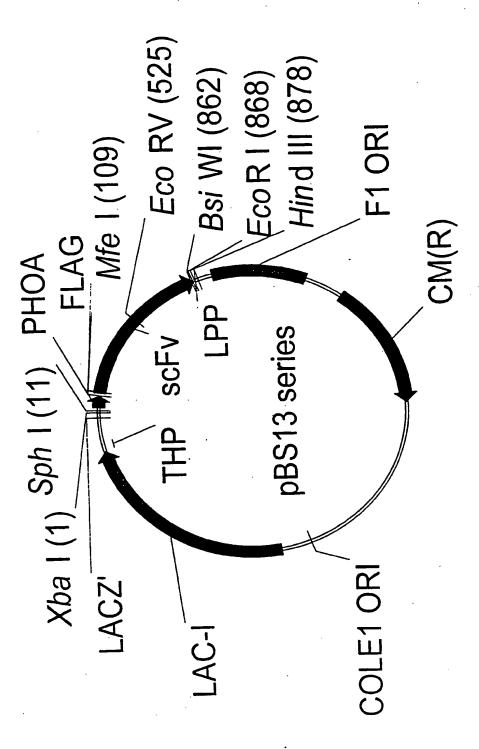
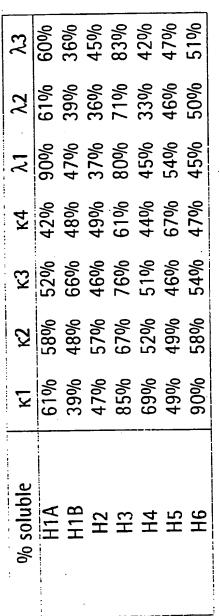


Figure 39: functional map of expression vector series pBS13

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Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)





Total amount		?	Ć	7.5	11	7.2	7.2
compared to H3K2	<u>-</u>	Z	2	<b>†</b>	٧.	77	3
H1A	289%	94%	166%	272%	20%	150%	78%
H18	219%	122%	89%	139%	117%	158%	101%
H2	186%	223%	208%	182%	126%	%09	97%
H3	20%	-	71%	54%	23%	130%	47%
H4	37%	55%	%09	77%	195%	107%	251%
H5	%86	201%	167%	83%	93%	128%	115%
H6	65%	117%	89%	109%	299%	215%	278%

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Figure 40: Expression data for HuCAL scFvs (pBS13, 30°C)

Soluble amount	Ş	ż	5	72	11	3.2	73
compared to H3K2	<u>-</u>	لا	2	<del>*</del>	-₹	7,5	3
H1A	191%	880%	121%	122%	26%	211%	· 0/09 /
H1B	124%	95%	83%	107%	79%	142%	230%
H2	126%	204%	139%	130%	%99	20%	0/00/
H3	. 63%	1	81%	49%	%69	143%	61%
H4	40%	47%	49%	54%	95%	55%	125%
HS	%69	158%	116%	80%	72%	84%	84%
9H	85%	122%	87%	17%	162%	162%	212%
	McPC						•
soluble	38%	•					
%H3k2 total	117%						
%H3k2 soluble	<sub>40</sub> 69						

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